JAN 06 2005

1/45

Fig. 1

drIndyl sequence (total 2602)

(ORF: 258 - 1976)
SEQ ID NO: 1

TTCACCGTTTCCGAATCGGACGAACCGGGCGTGATTGCTCTCCTGCTGCTTTCGAGATCGGAGTCCCGAT
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TACTTGTTATCAACTGGGAAGCGGAGATACATAGCTCCGATATTCCTGTGAAAGCCAGACAAACGGATAC
CAACGAACAATCGCCATATCTACACGCCACCGCCACTGGACATCAAAATGGAAATTGAAATTGGCGAACA
ACCCCAGCCTCCGGTGAAGTGCTCCAACTTCTTCGCTAACCACTGGAAGGGATTGGTTGTGTTCCTGGTG
CCGCTGCTATGTCTGCCTGTTATGCTGCTAAACGAAGGCGCCGAATTTCGGTGCATGTACCTCCTTTTGG
TAATGGCCATATTTTGGGTTACGGAAGCCTTGCCTCTCTATGTGACGTCCATGATACCGATTGTGGCCTT
CCCAATAATGGGTATAATGAGCTCGGATCAGACTTGCCGCTTGTACTTCAAGGATACGCTGGTGATGTTC
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GCTCAGGGTGTCTGCAAAATCAACCATGAGCCTCAATACCAAATCGTTGGAGGCAACAAGAAAAACAACG
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GGTCCCATGTCCATTCACGAGATCCAAGTGATGATTCTGTTCATTTTTATGGTTGTGATGTACTTCACCC
GCAAGCCCGGCATCTTTTTGGGATGGGCCGATTTGCTGAATTCCAAGGACATTCGTAACTCTATGCCCAC
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Peptide seq (total 572)

SEQ ID NO: 2

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GIAYASSLGGCGTIIGTATNLTFKGIYEARFKNSTEQMDFPTFMFYSVPSMLVYTLLTFVFLQWHFMGLW
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Fig. 2A

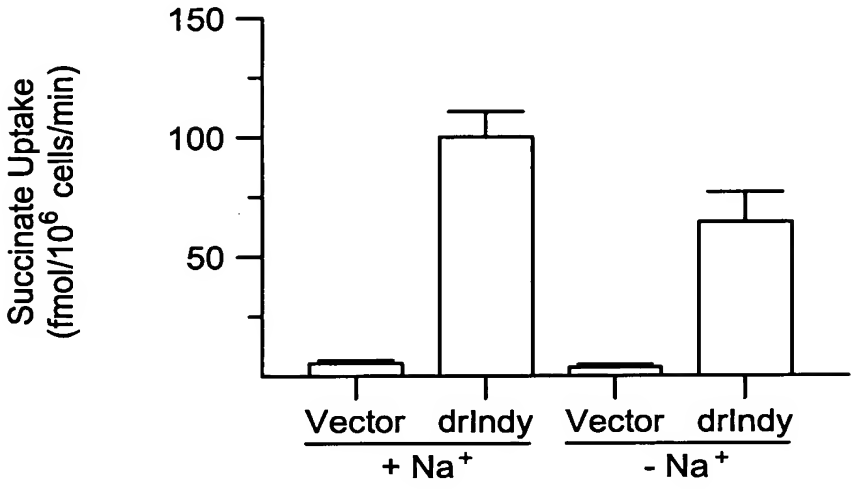
150
100
50
Succinate Uptake
(fmol/10^6 cells/min)
Vector
drIndy
Vector
drIndy
+ Na+
- Na+

Fig. 2B

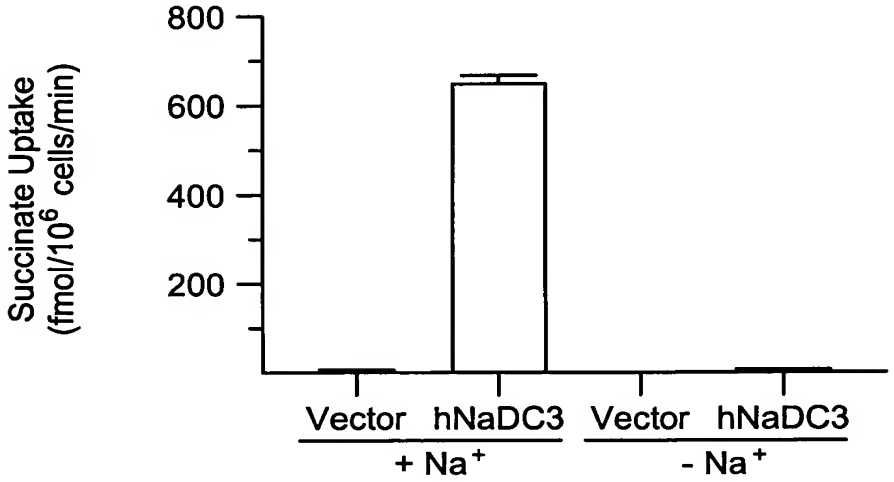
800
600
400
200
Succinate Uptake
(fmol/10^6 cells/min)
Vector
hNaDC3
Vector
hNaDC3
+ Na+
- Na+

Fig. 3

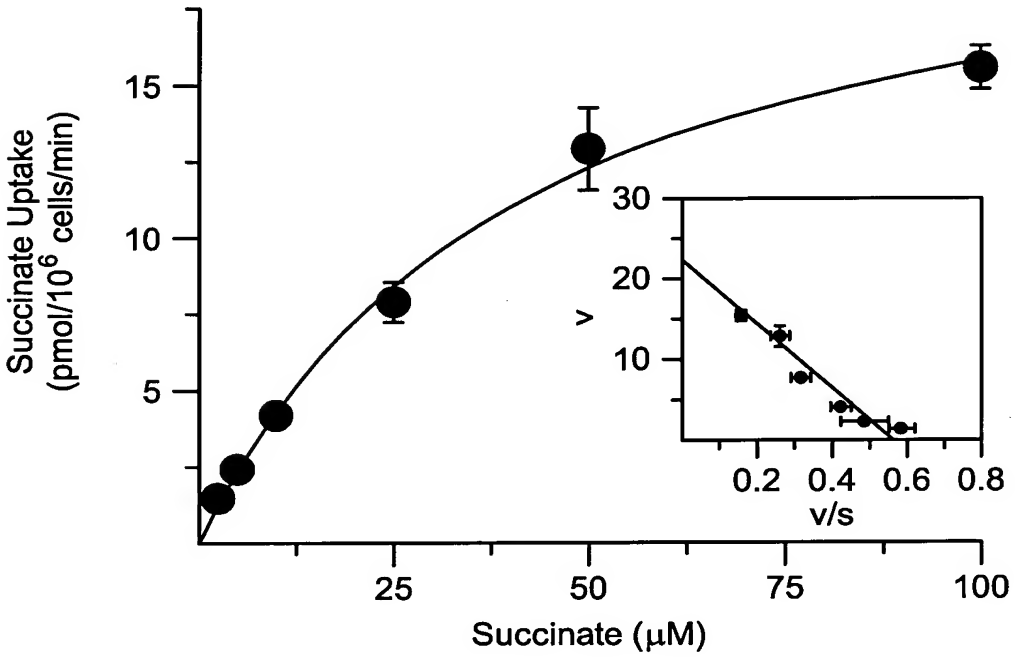
Succinate Uptake
(pmol/10^6 cells/min)
15
10
5
25
50
75
100
Succinate (μM)
30
20
10
v
0.2
0.4
0.6
0.8
v/s

Fig. 4A

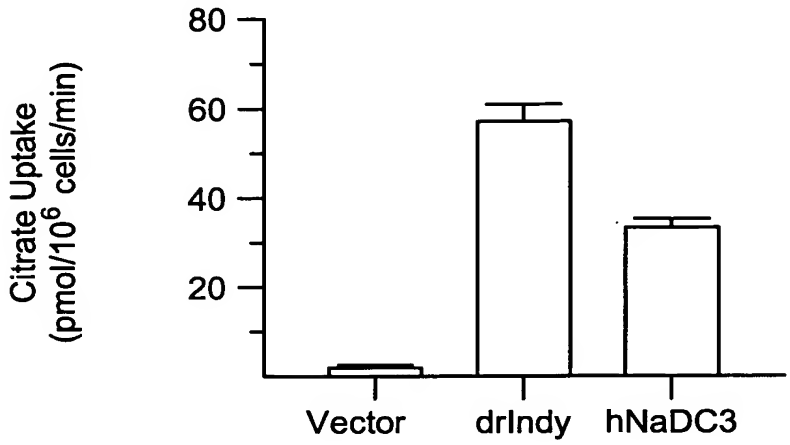
80
60
40
20
Citrate Uptake
(pmol/10^6 cells/min)
Vector
drIndy
hNaDC3

Fig. 4B

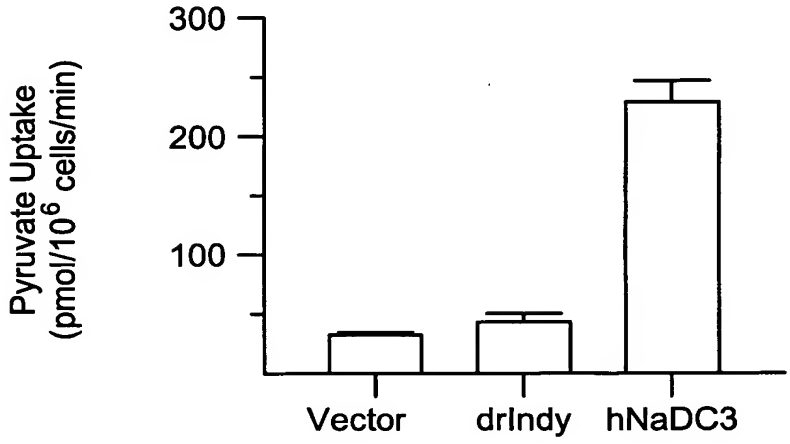
300
200
100
Pyruvate Uptake
(pmol/10^6 cells/min)
Vector
drIndy
hNaDC3

Fig. 5

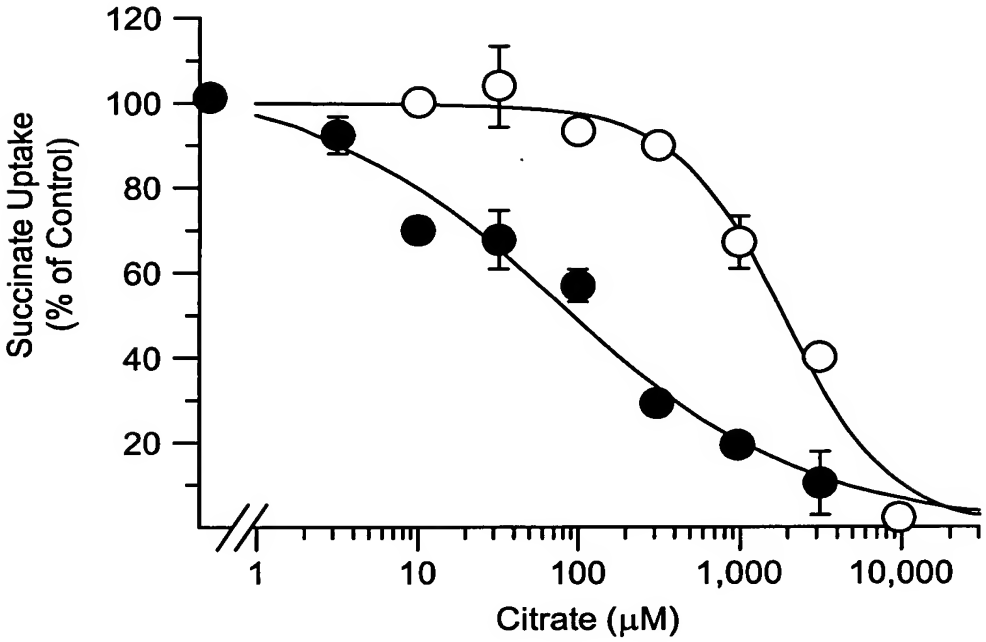
120
100
80
60
40
20
Succinate Uptake
(% of Control)
1
10
100
1,000
10,000
Citrate (μM)

Fig. 6A

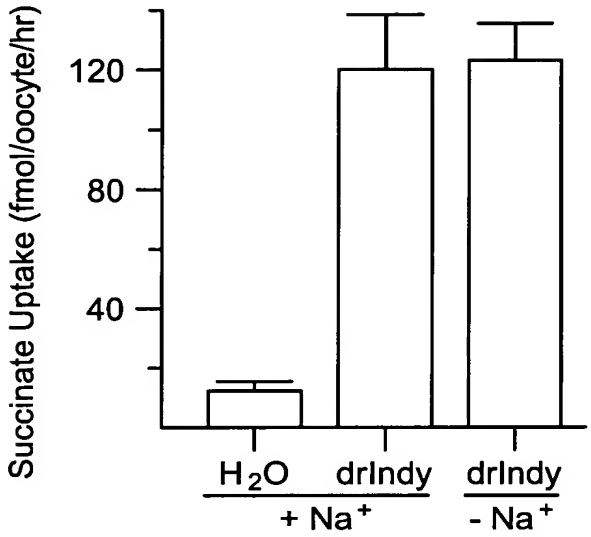

Fig. 6B

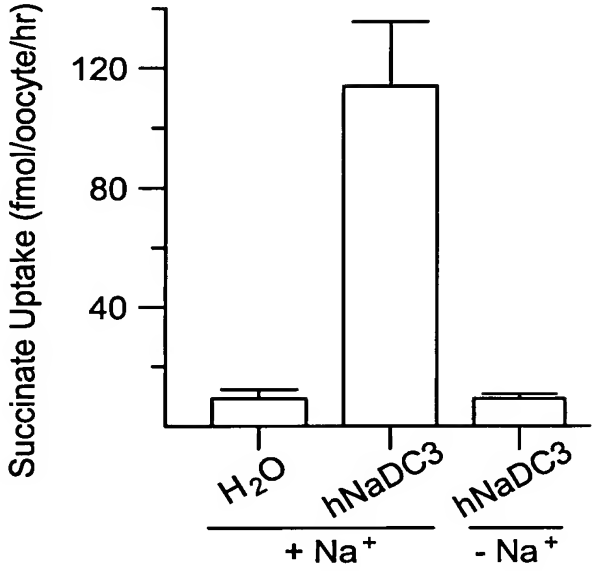

Fig. 6C

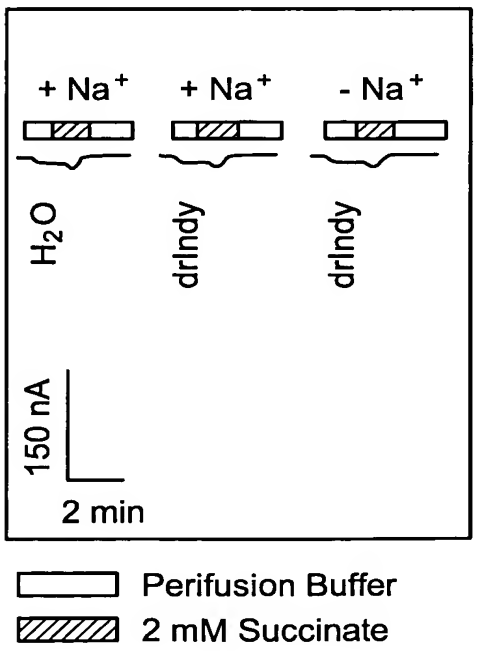

Fig. 6D

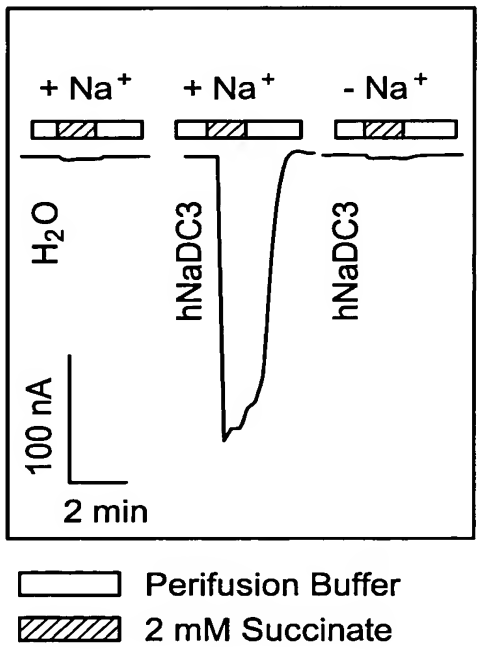

Fig. 7

Rat INDY seq.
(3191 nt + 63 nt polyA)
SEQ ID NO: 3

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TATGTTATAATCCTCATGGCCATCTACTGGTGCACAGATGTCATCCCAGTGGCTATCACTTCCCTCCTGC
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CAACATGCTGTTCCTGGGCAGTCTCATTGTGGCCACGGCTGTGGAACGTTGGGAACTTCATAAGAGGATT
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CCTTCCTGTCCATGTGGATCAGCAATACTGCCACCACGGCCATGATGATACCCATTGTGGAGGCCATGCT
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CCTTGTCCTTCAGGGATGCTCTCTTCCTTGCTTAATTTGCTCTGAAAAGAAGCATGAGTGGGGAGATAAG
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CAAGTATGTGTCTGGCTCCTTGGGAGGGATGGCTCCTGACCATACTGTCGAAGGCTTGCTCTTGTCAAAT
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AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

(572 aa)
SEQ ID NO: 4

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MNLCVCYAASIGGTATLTGTGPNVVLLGQMQELFPDSKDVMNFASWFAFALPNMLLMLVMAWLWLLCFYM
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GFAMAKGCETSGLSEWMARQMEPLSSVRPAIITLILSCIVAMTTECTSNVATTTLFLPIFASMARSIGIH
PLYVMIPCTLSASLAFMLPVATPPNAIVFAYGHLKVIDMVKTGLVMNILGIASVFLSVNTWGRAVFNLDK
FPDWANLTHINT

Fig. 8

rNaCT 1 ---MASAKTYVTKFKSFVILFFAPILLLPLIILVPDKFARCAYVIILMAIYWCTDVIPVA
rNaDC1 1 ---MATCWPALWAYRFYLIVLCLPIFLLPLPLIVQTKEAYCAYSIILMALLWCTEALPLA
rNaDC3 1 MAALAALAKKVWSARRLLVLLLVPLALLPIILFALPPKEGRCLYVILLMAVYWCTEALPLS
rNaCT 58 ITSLLPVLLFPLLKVLDSKQVCVQYMTDTNMLFLGSLIVATAVERWELHKRIALRMLLFV
rNaDC1 58 VTALFPIVLFPLMGIMDASEVCIEYFKDTNILFVGGLMVAIAVEHWNLHKRIALQVLLII
rNaDC3 61 VTALLPILLFPFMGILPSSKVCPQYFLDTNFLFLSGLIMASAIEERNLHRRIALKVLMLV
rNaCT 118 GTKPSRLMLGFMFVTAFLSMWISNTATTAMMIPIVEAMLEQMVA---TNVAVDASQR--T
rNaDC1 118 GVRPALLLLGFMLVTAFLSMWISNTATTAMMVPIGHAVLEQLQG---SKKDVEGGNNNPT
rNaDC3 121 GVQPARLILGMMVTTSFLSMWLSNTASTAMMLPIASAILKSLFGQRDTRKDLPREGEDST
rNaCT 173 MELLDKN----------KASELPGSQVVFEDPS-VQKQEDEETKN-MYKAMNLCVCYAA
rNaDC1 175 FELQEECPQ--------KEVTKLDNGQPVSAPSE-PRTQKTQEHHR-FSQGLSLCICYSA
rNaDC3 181 AAVRGNGLRTVPTEMQFLASSEGGHAEDVEAPLELPDDSKEEEHRRNIWKGFLISIPYSA
rNaCT 220 SIGGTATLTGTGPNVVLLGQMQELFPDSKDVMNFASWFAFALPNMLLMLVMAWLWLLCFY
rNaDC1 225 SIGGIATLTGTTPNLVLQGQVNSLFPQNGNVVNFASWFGFAFPTMIILLLLAWLWLQVLF
rNaDC3 241 SIGGTATLTGTAPNLILLGQLKSFFPQC-DVVNFGSWFIFAFPLMLLFLLVGWLWISFLY
rNaCT 280 MRPNLKKTCICCGRKKKDTEKIASKVLYEEYRKLGPLSYAECNVLFCFGLLIILWFSRDP
rNaDC1 285 LGVNFRKN-FGFGEGEEERKQAAFQVIKTQYRLLGPMSFAEKTVTVLFVLLVVLWFTREP
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rNaCT 340 GFMPGW-LSIAWIEGNTKHVTDATVAIFVAILLFIVPSQKPKFNFSRQTEEERKTPFYPP
rNaDC1 344 GFFPGWGDTVFANEKGQSMASDGTVAIFISLVMFIIPSKIPGLMQDPKKPGKLKA---PP
rNaDC3 360 KFIPGW-ASLFAP----GFVSDAVTGVAIVTILFFFPSQKPSLKWWFDFKAPNSE---TE
rNaCT 399 PLLNWKVTQEKVPWGIVLLLGGGFAMAKGCETSGLSEWMARQMEPLSSVRPAIITLILSC
rNaDC1 401 AILLTWKTVNDKMPWNIVILLGGGFALAKGSEQSGLSEWLGDKLTPLQHIPPSATAVILCL
rNaDC3 412 PLLSWKKAQETVPWNIILLLGGGFAMAKGCEESGLSAWIGGQLHPLEHVPPLLAVLLITV
rNaCT 459 IVAMTTECTSNVATTTLFLPIFASMARSIGIHPLYVMIPCTLSASLAFMLPVATPPNAIV
rNaDC1 461 LIAIFTECTSNVATTTLFLPILASMAQAICLHPLYVMLPCTLAASLAFMLPVATPPNAIV
rNaDC3 472 VIAFFTEFASNTATIIIFLPVLAELAIRLHVHPLYLMIPGTVSCSYAFMLPVSTPPNSIA
rNaCT 519 FAYGHLKVIDMVKTGLVMNILGIASVFLSVNTWGRAVFNLDKFPDWAN-------LTH--
rNaDC1 521 FSFGGLKVSDMARAGFLLNIIGVLAITLSINSWSIPIFKLDTFPSWAHSNTSQCLLNP--
rNaDC3 532 FSTGHLLVKDMVRTGLLMNLMGVLLLSLAMNTWAQAIFQLGTFPDWANTHAANVTALPPA
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rNaDC1 579 -SNSTVPGGL
rNaDC3 592 LINNTVQTL-

Fig. 9

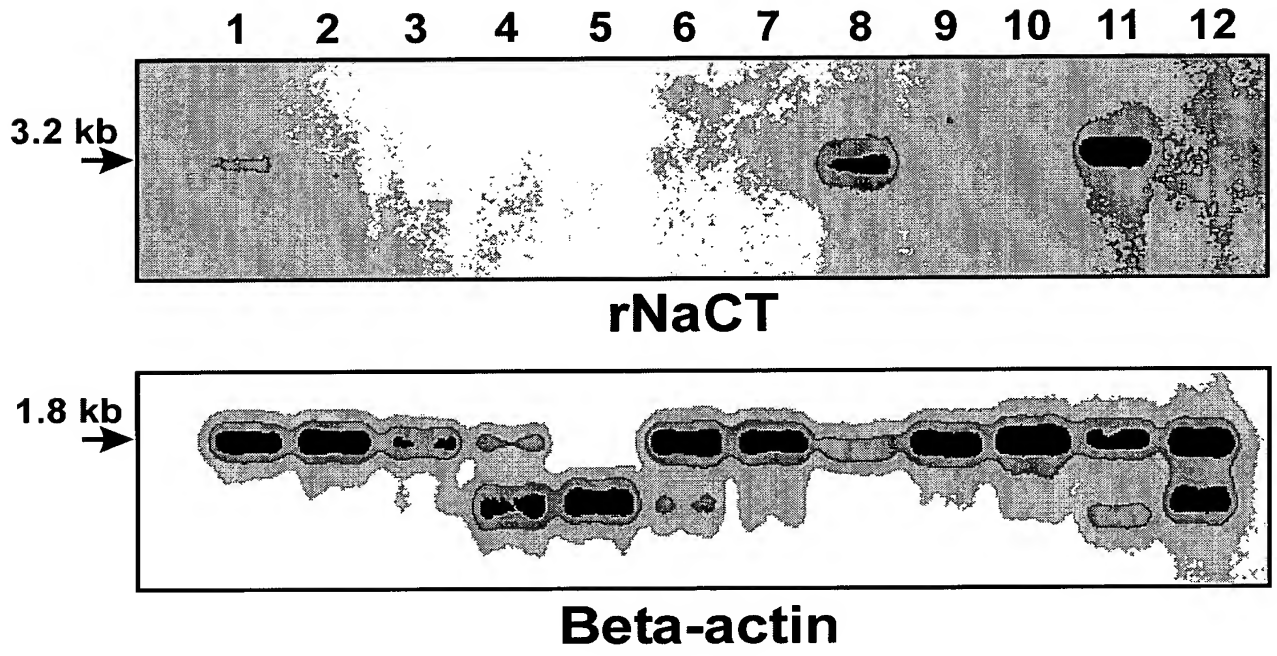

Fig. 10A

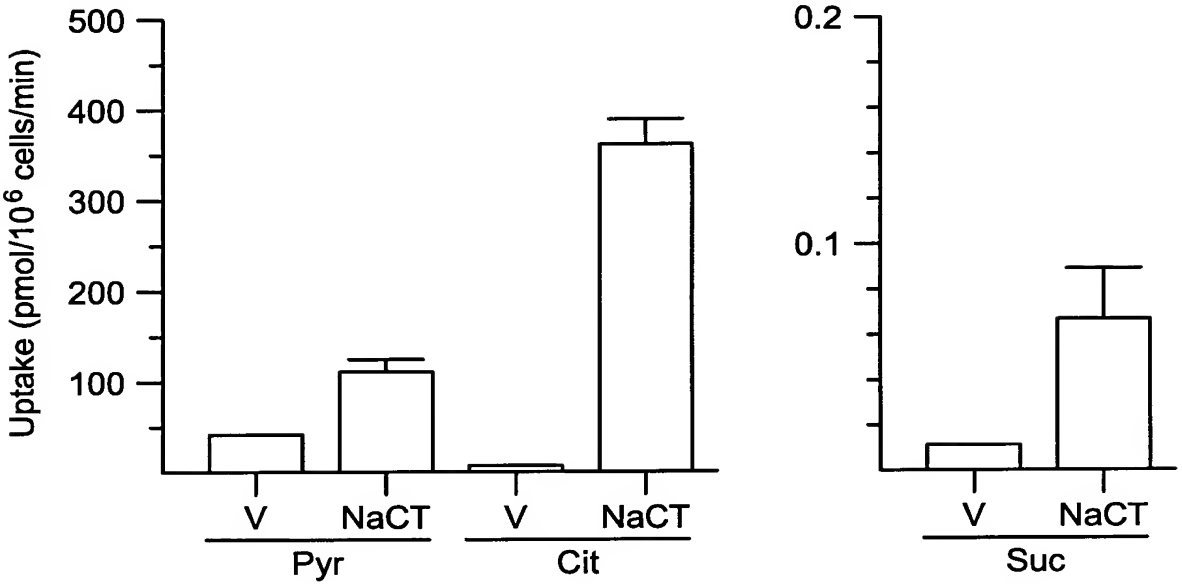

Fig. 10B

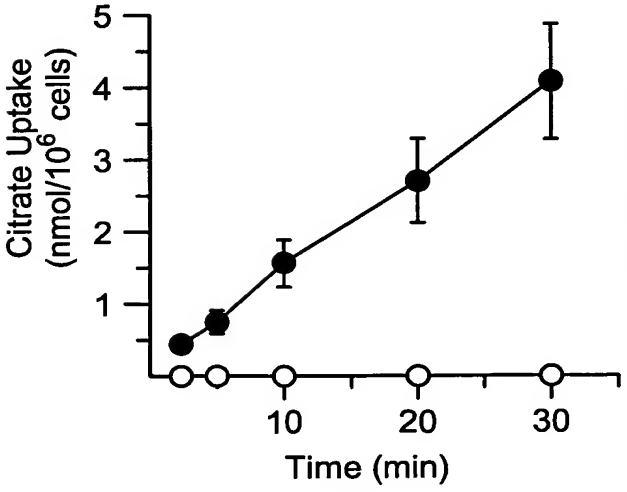

Fig. 10C

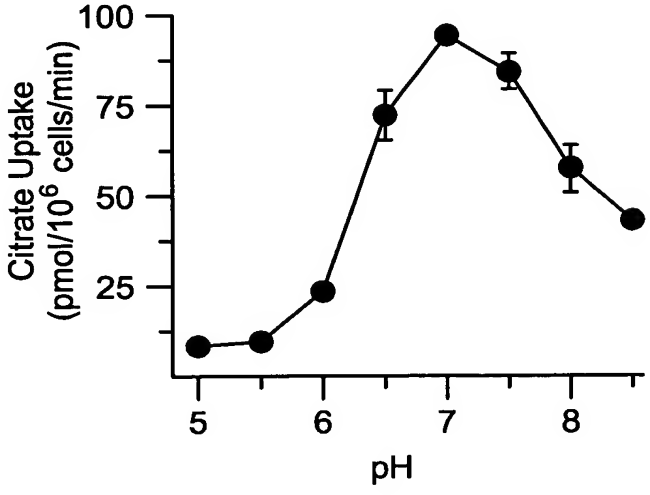

Fig. 11A

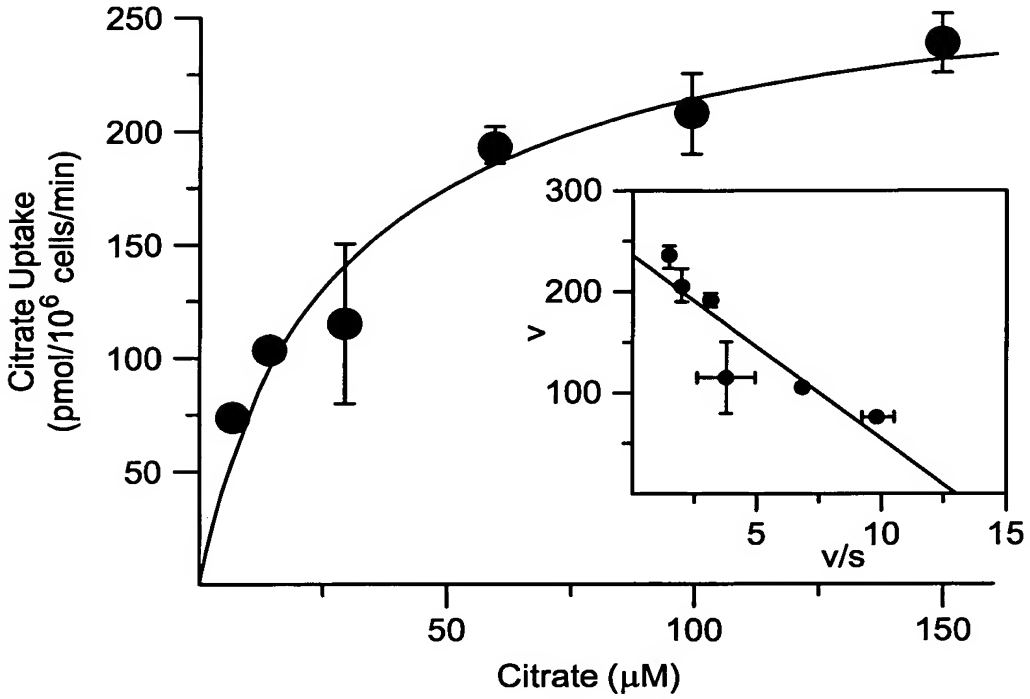

Fig. 11B

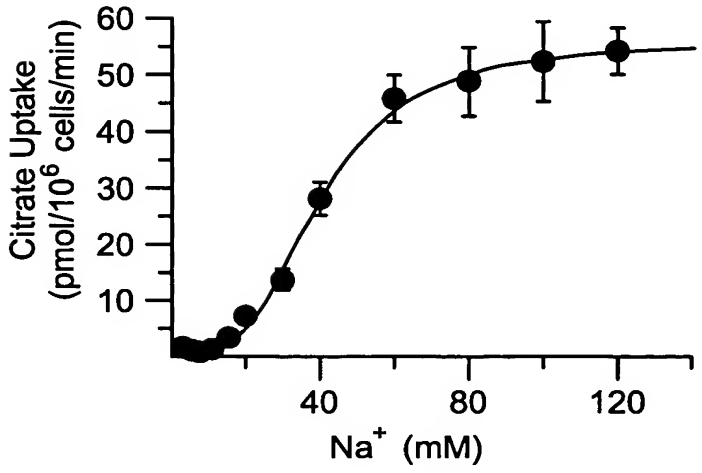

Fig. 11C

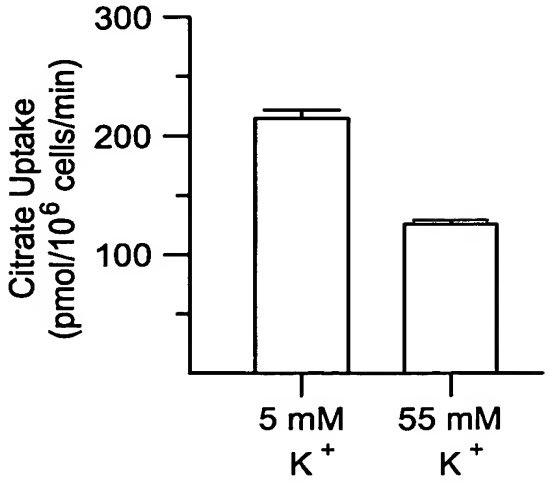

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Fig. 12A

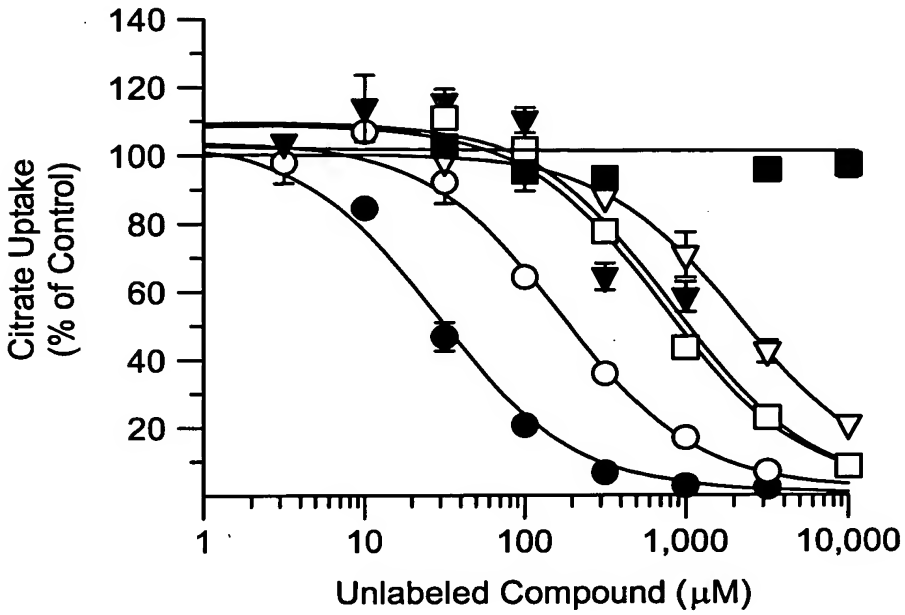


Fig. 12B

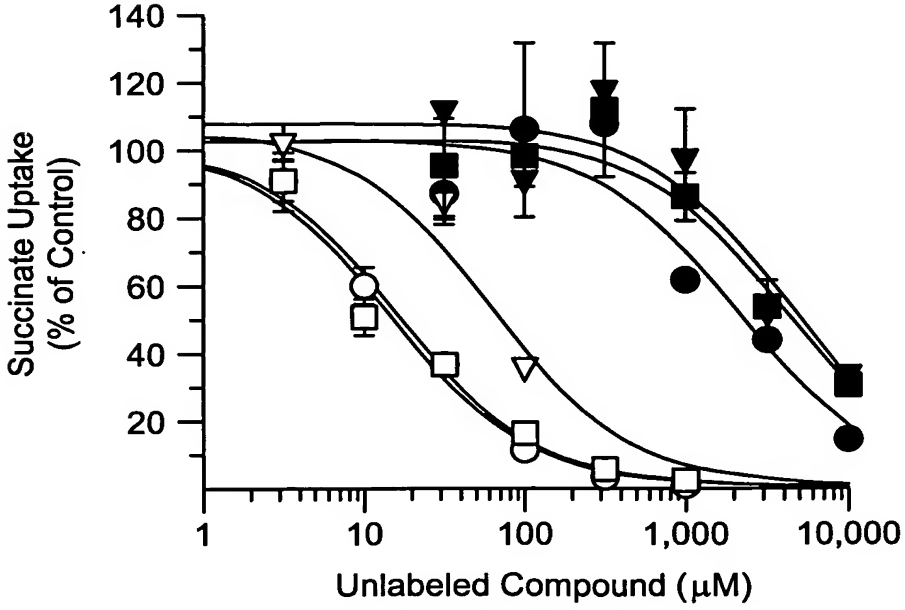


Fig. 13A

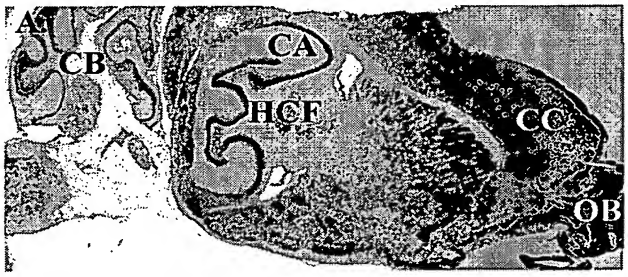


Fig. 13B

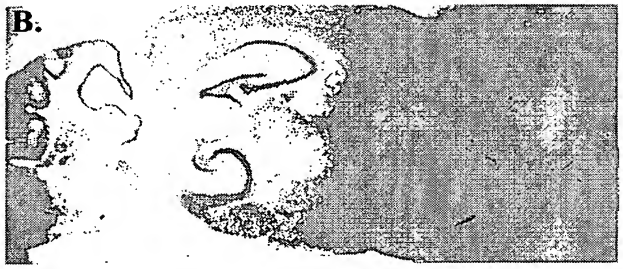


Fig. 13C

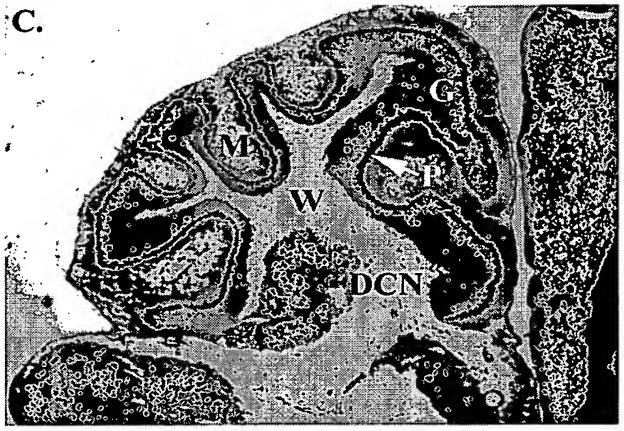
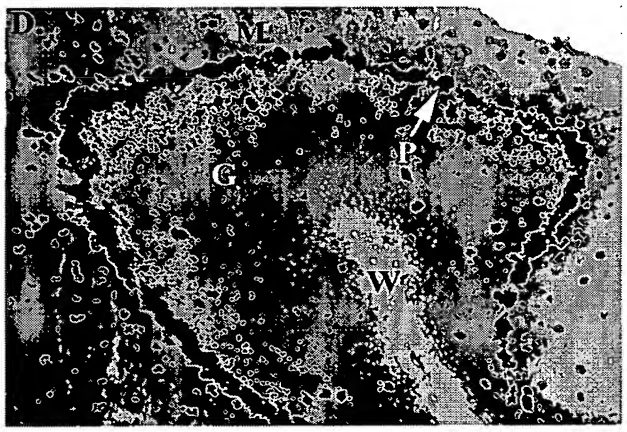


Fig. 13D



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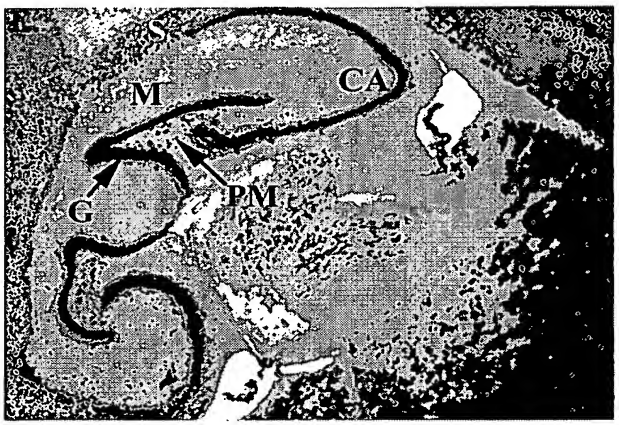

Fig. 13F

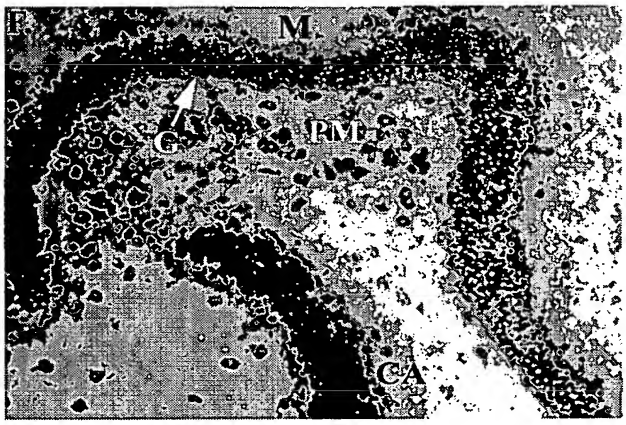

Fig. 14

Human NaCT sequence
(3207 nt + 41 nt polyA)
ORF: 13-1719 (total 1707 nt)
SEQ ID NO: 5

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Amino acid sequence(568 aa)
SEQ ID NO: 6

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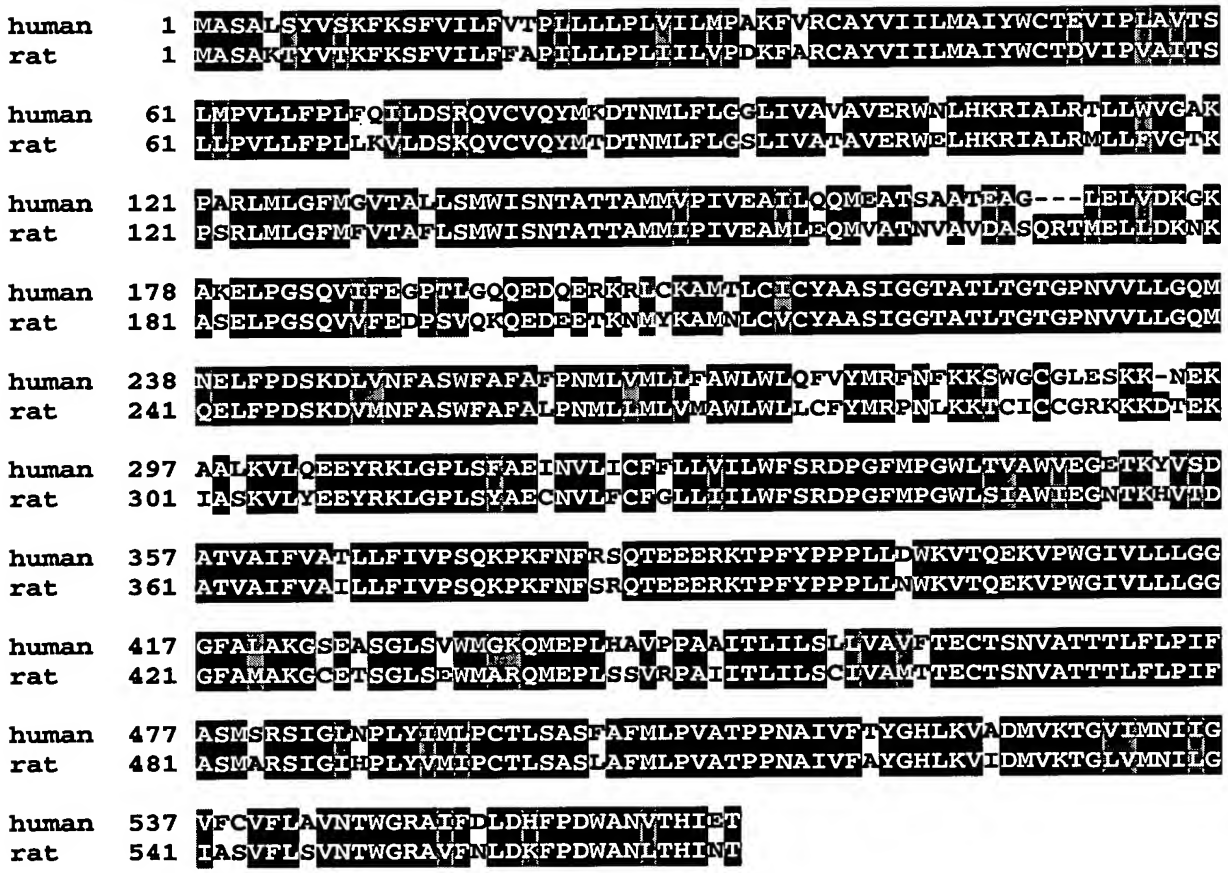
Fig. 15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rat 61 LLPVLLFPLLKVLDSKQVCVQYMTDTNMLFLGSLIVATAVERWELHKRIALRMLLFVGTK
human 121 PARLMLGFMGVTALLSMWISNTATTAMMVPIVEAILQQMEATSAATEAG---LELVDKGK
rat 121 PSRLMLGFMFVTAFLSMWISNTATTAMMIPIVEAMLEQMVATNVAVDASQRTMELLDKNK
human 178 AKELPGSQVTFEGPTLGQQEDQERKRLCKAMTLCICYAASIGGTATLTGTGPNVVLLGQM
rat 181 ASELPGSQVVFEDPSVQKQEDEETKNMYKAMNLCVCYAASIGGTATLTGTGPNVVLLGQM
human 238 NELFPDSKDLVNFASWFAFAFPNMLVMLLFAWLWLQFVYMRFNFKKSWGCGLESKK-NEK
rat 241 QELFPDSKDVMNFASWFAFALPNMLLMLVMAWLWLLCFYMRPNLKKTCICCGRKKKDTEK
human 297 AALKVLQEEYRKLGPLSFAEINVLICFFLLVILWFSRDPGFMPGWLTVAWVEGETKYVSD
rat 301 IASKVLYEEYRKLGPLSYAECNVLFCFGLLIILWFSRDPGFMPGWLSIAWIEGNTKHVTD
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rat 421 GFAMAKGCETSGLSEWMARQMEPLSSVRPAIITLILSCIVAMTTECTSNVATTTLFLPIF
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rat 481 ASMARSIGINPLYVMIPCTLSASLAFMLPVATPPNAIVFAYGHLKVIDMVKTGLVMNILG
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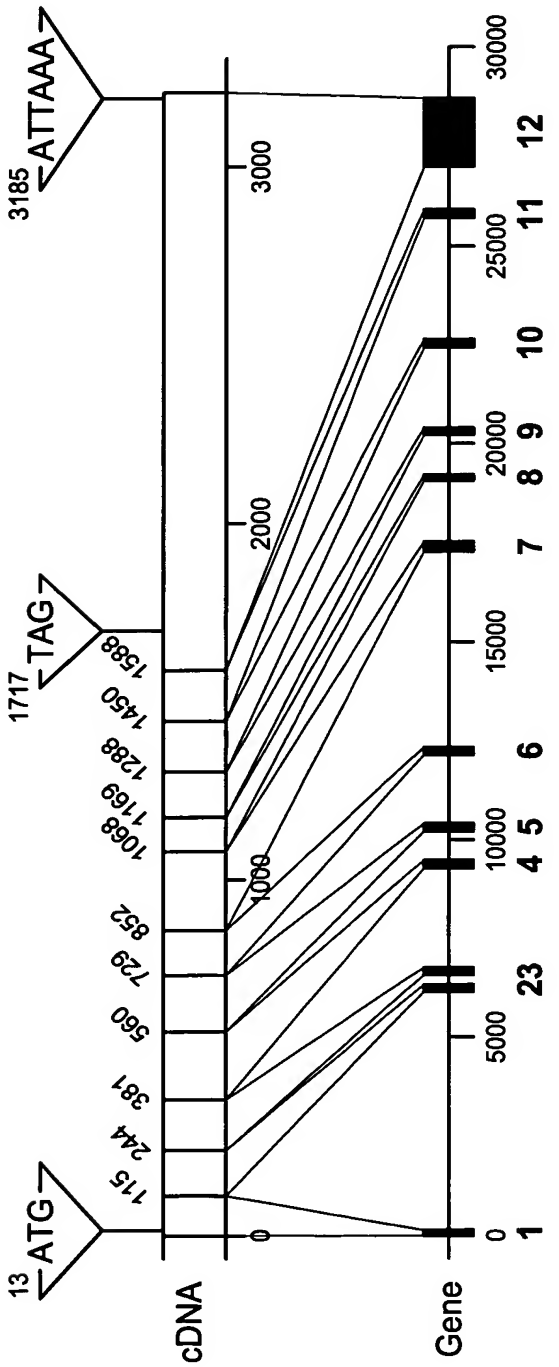
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852
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1000
cDNA
30000
25000
20000
15000
10000
5000
0
Gene
12
11
10
9
8
7
6
5
4
23
1

Fig. 16

Fig. 17A

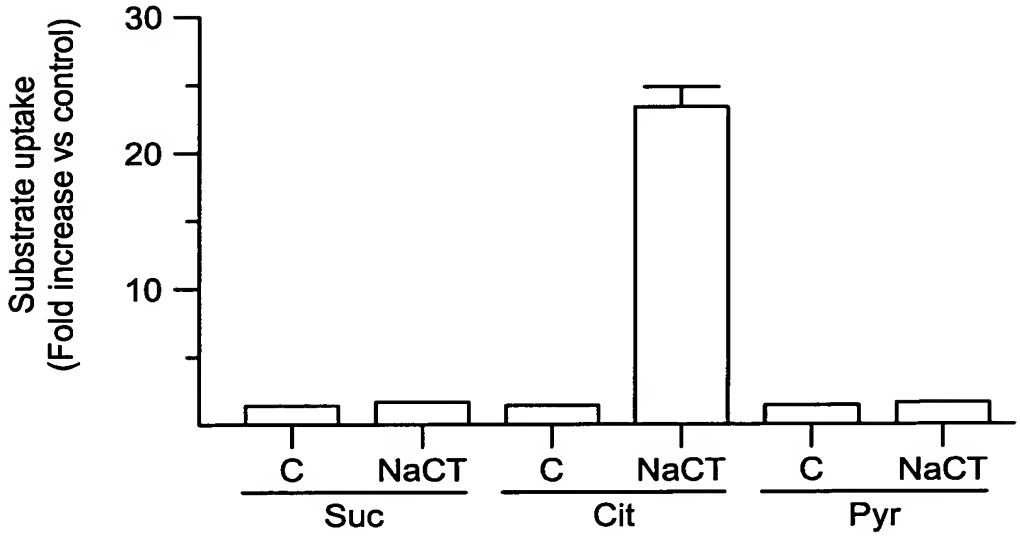


Fig. 17B

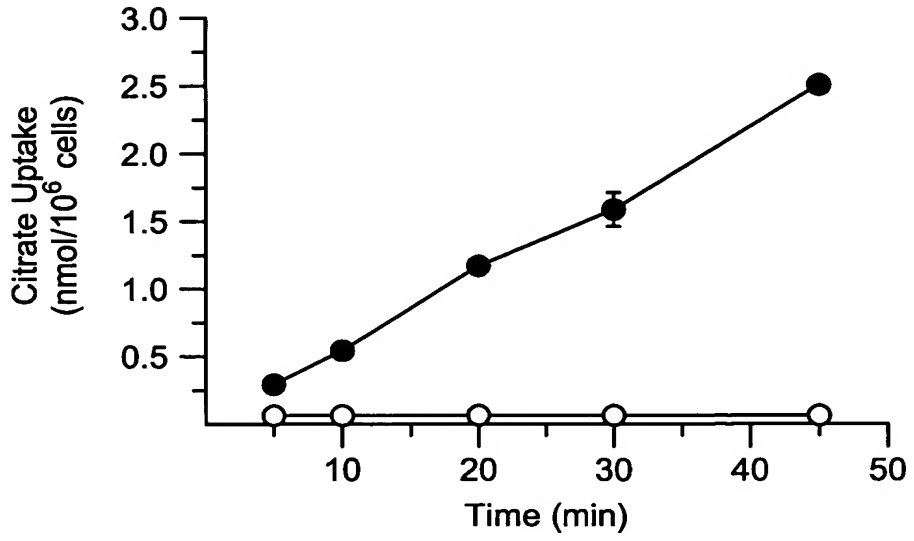


Fig. 18A

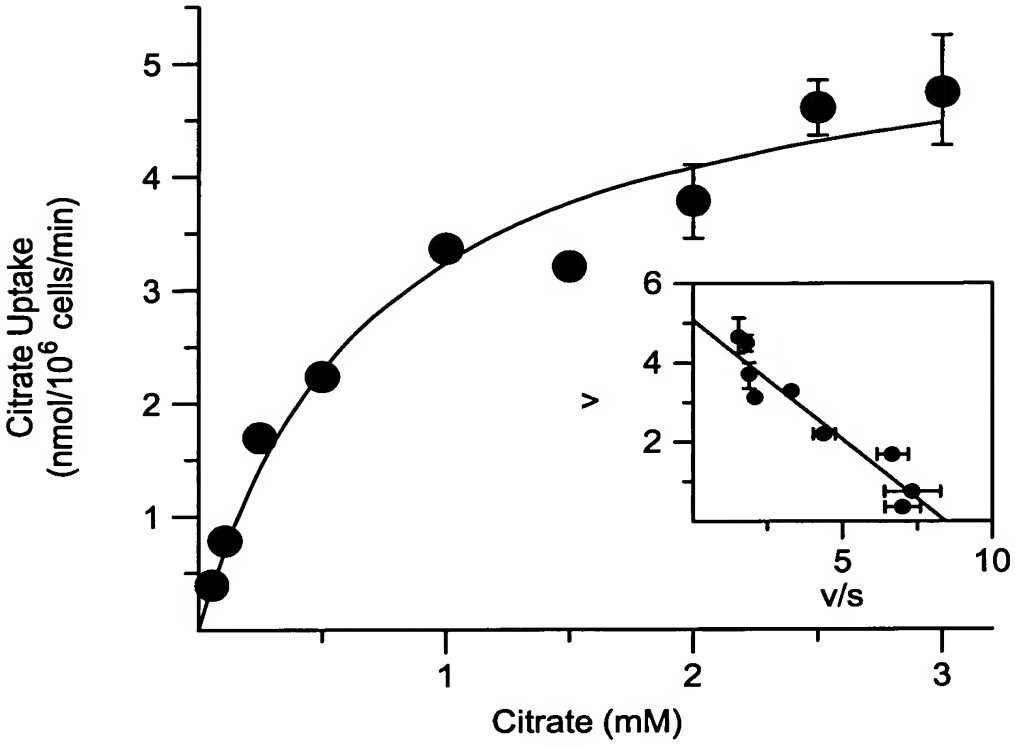


Fig. 18B

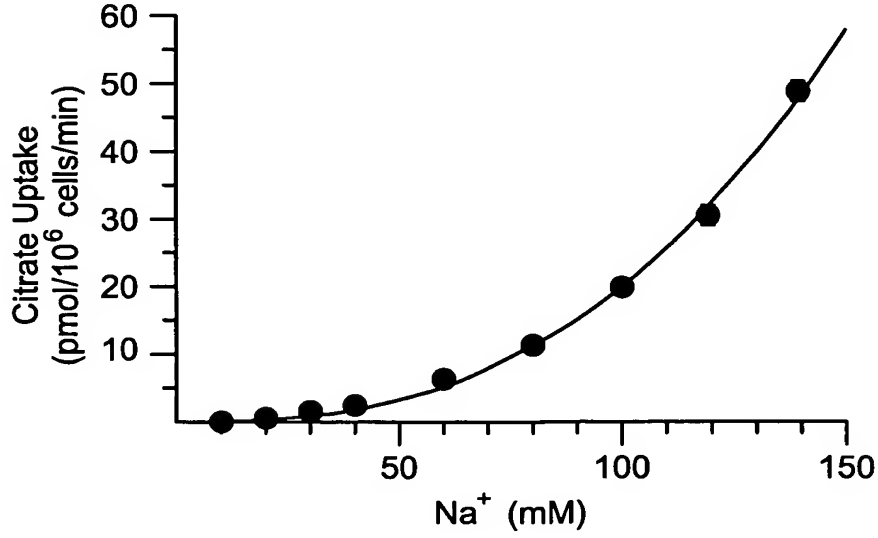
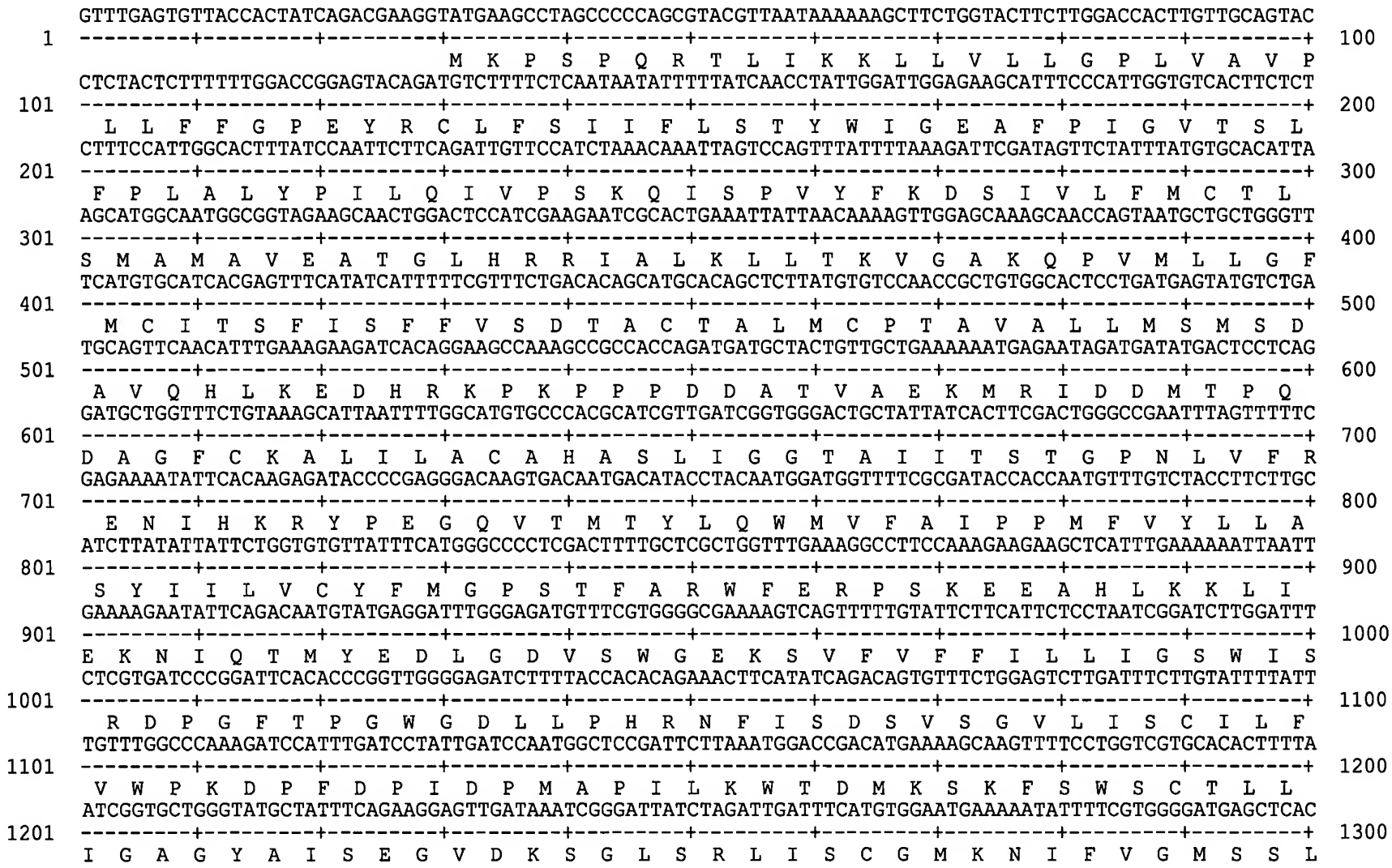


Fig. 19A

ceNaCT cDNA & Protein Sequences



Title: NaCT AS A TARGET FOR LIFESPAN EXPANSION AND WEIGHT REDUCTION
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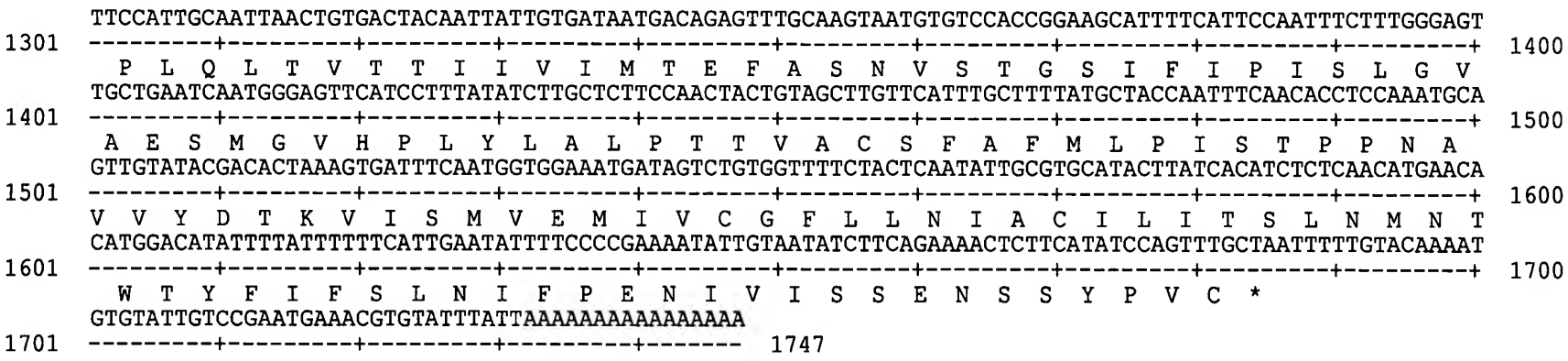
Fig. 19B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TGCTGAATCAATGGGAGTTCATCCTTTATATCTTGCTCTTCCAACTACTGTAGCTTGTTCATTTGCTTTTATGCTACCAATTTCAACACCTCCAAATGCA
1401 1500
A E S M G V H P L Y L A L P T T V A C S F A F M L P I S T P P N A
GTTGTATACGACACTAAAGTGATTTCAATGGTGGAAATGATAGTCTGTGGTTTTCTACTCAATATTGCGTGCATACTTATCACATCTCTCAACATGAACA
1501 1600
V V Y D T K V I S M V E M I V C G F L L N I A C I L I T S L N M N T
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1601 1700
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1701 1747

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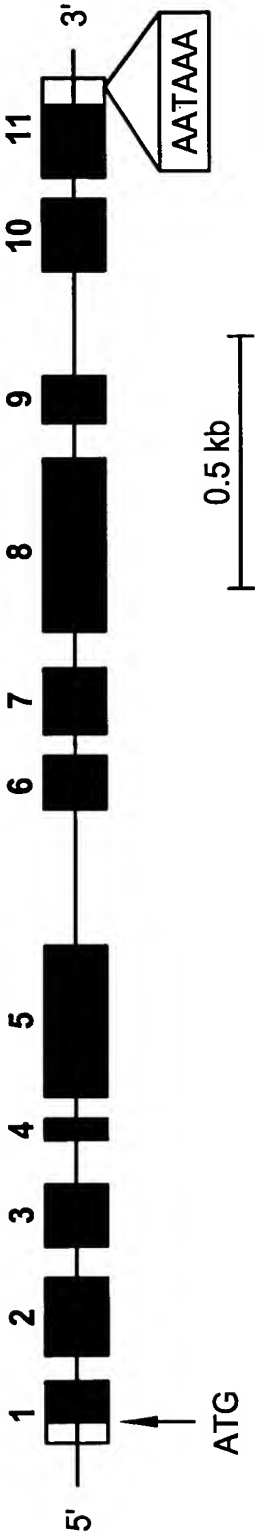

Fig. 20

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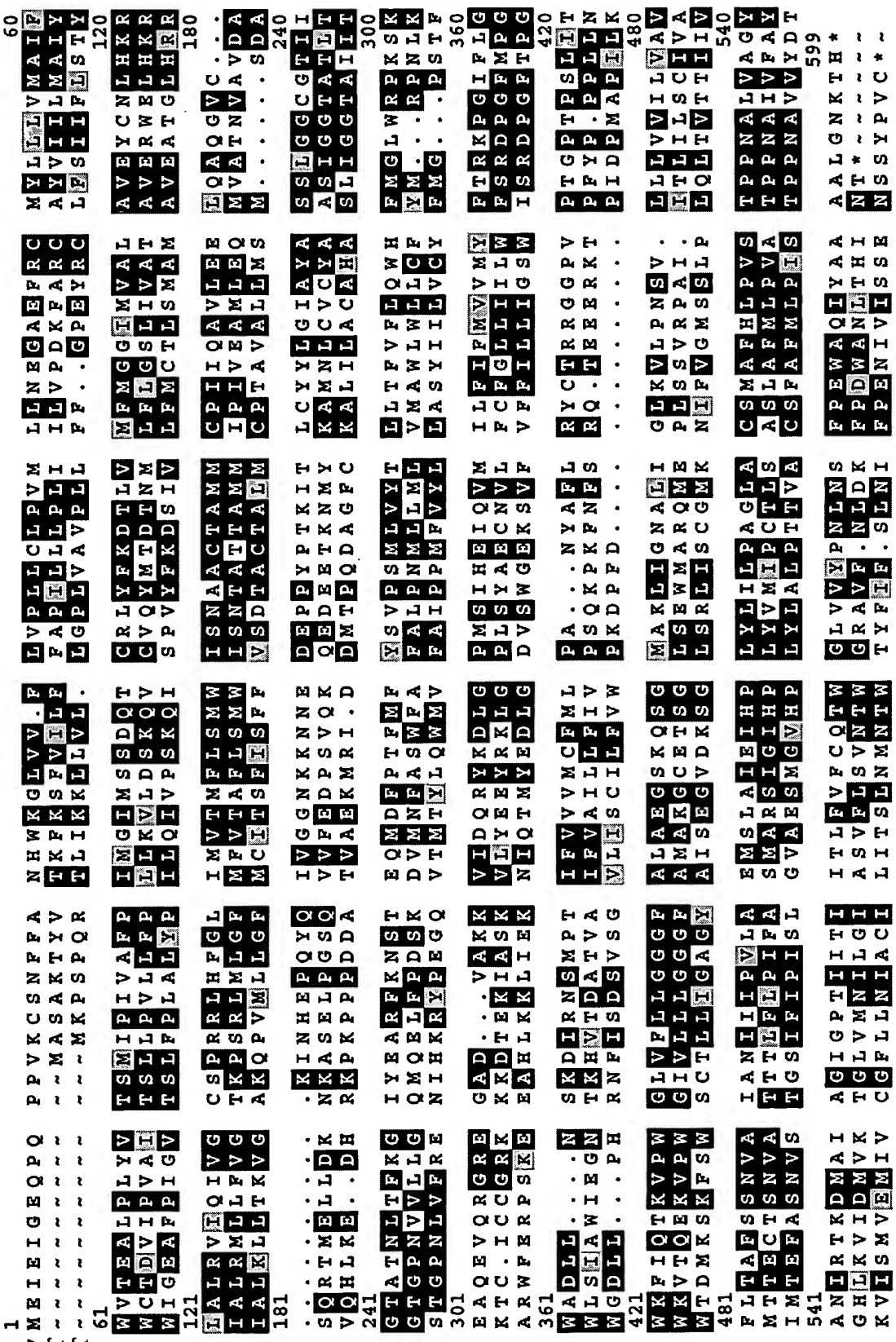

Fig. 21

Fig. 22A

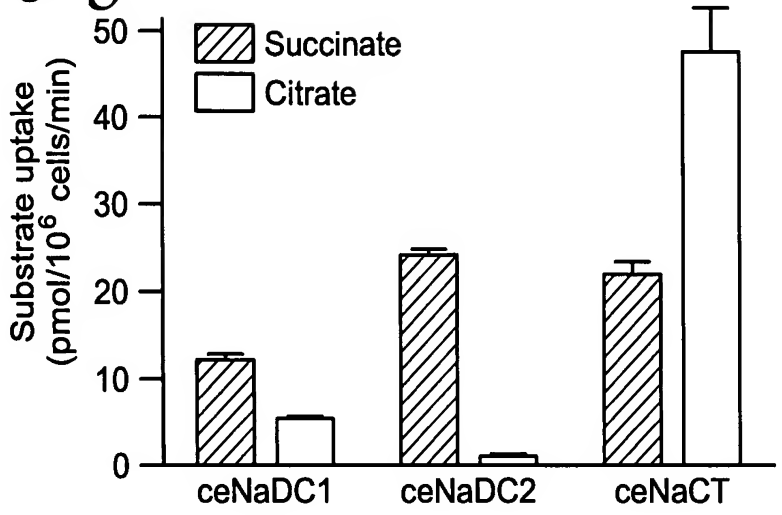

Fig. 22B

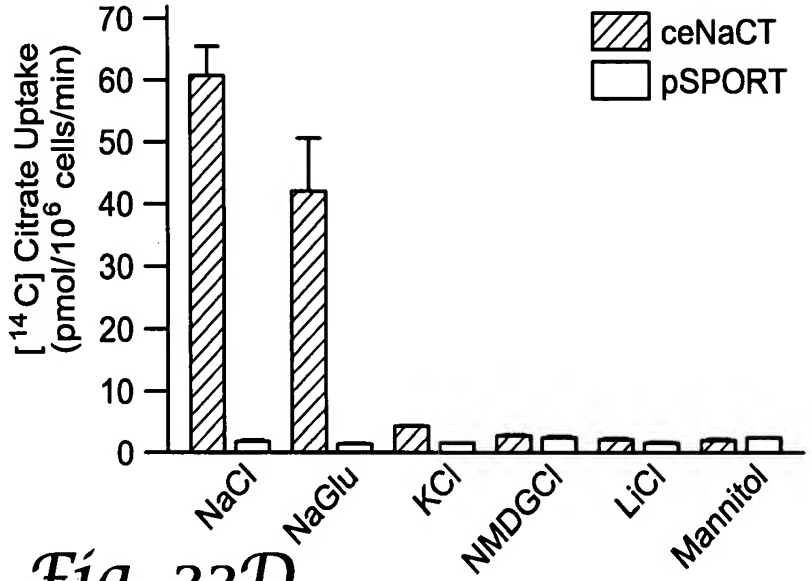

Fig. 22C

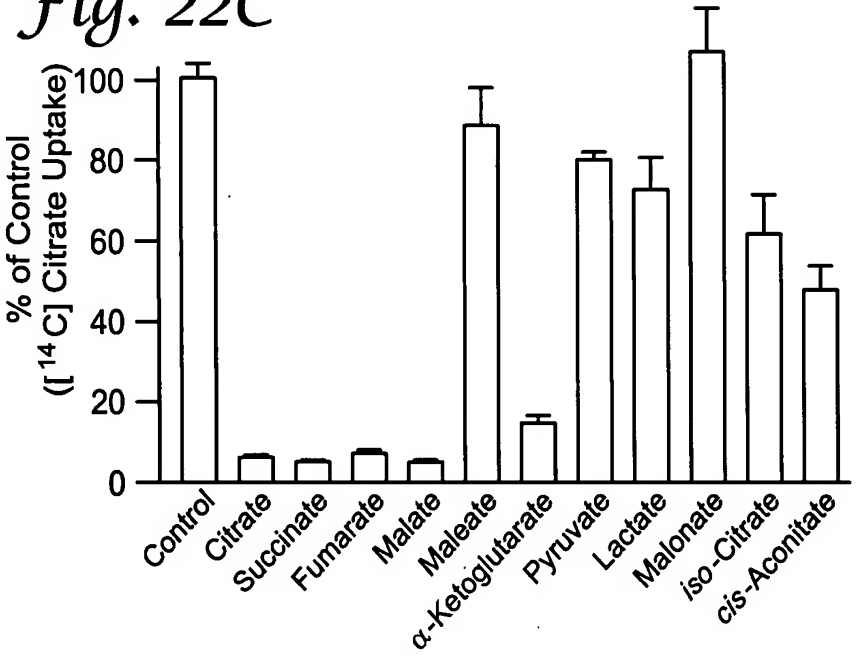

Fig. 22D

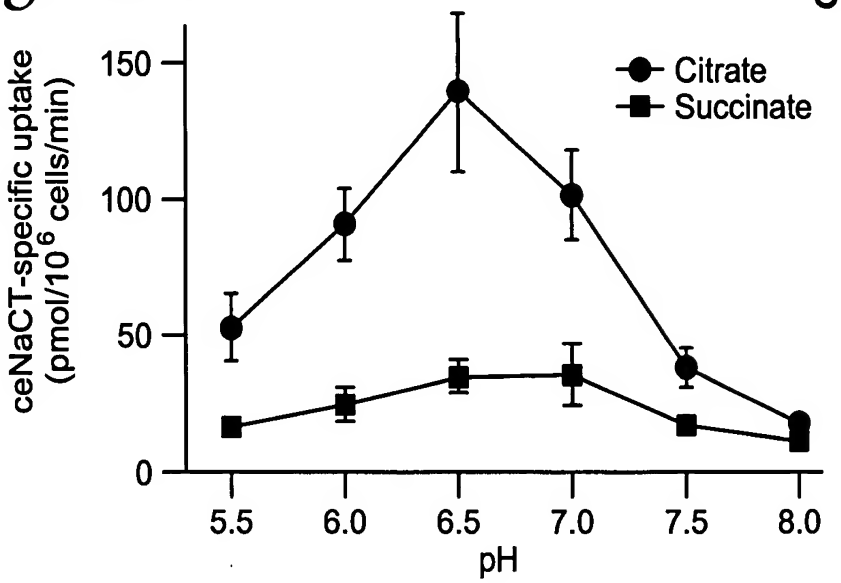

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Fig. 23A

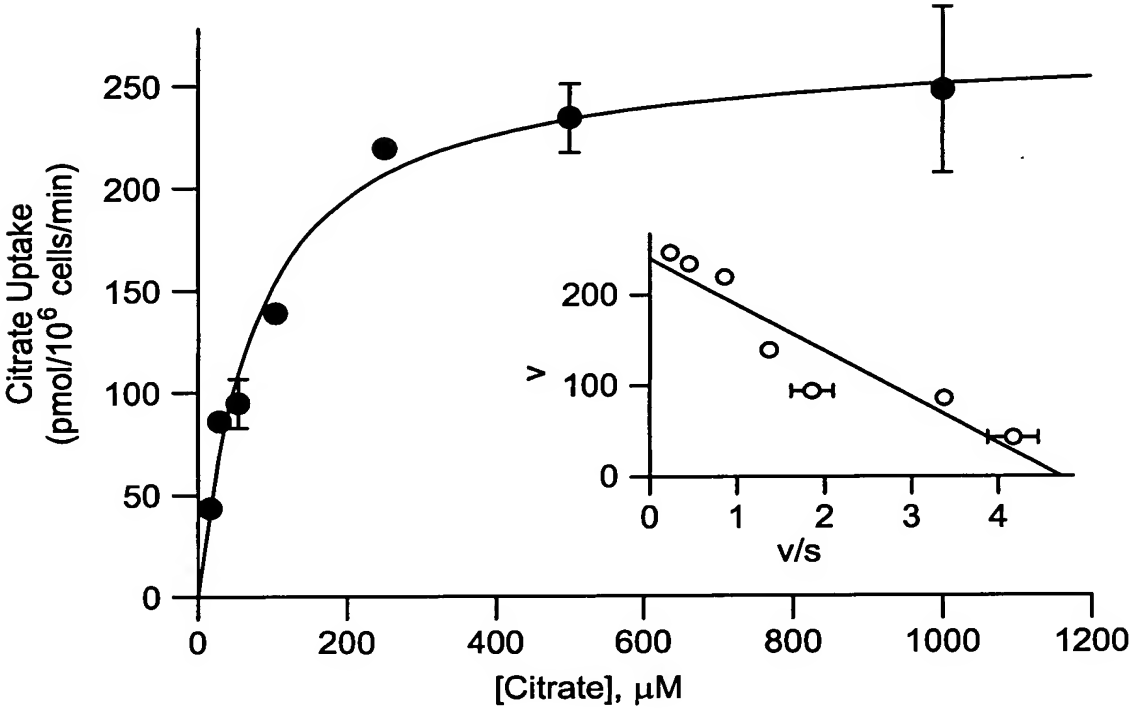


Fig. 23B

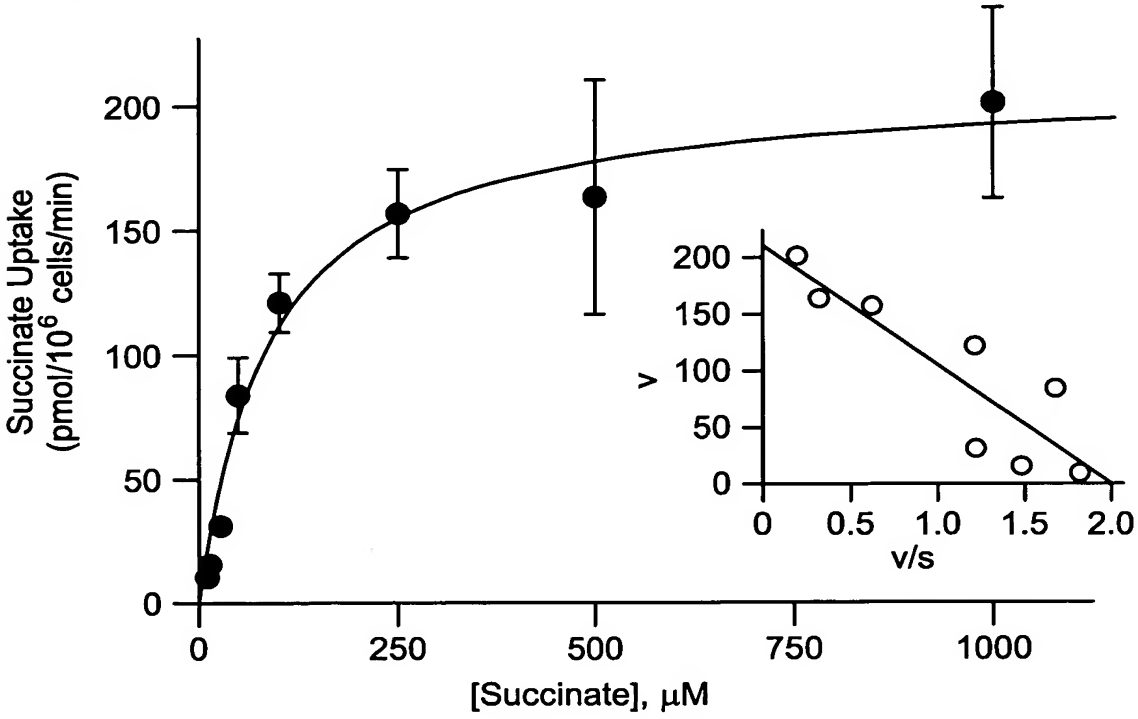


Fig. 24A

Fig. 24B

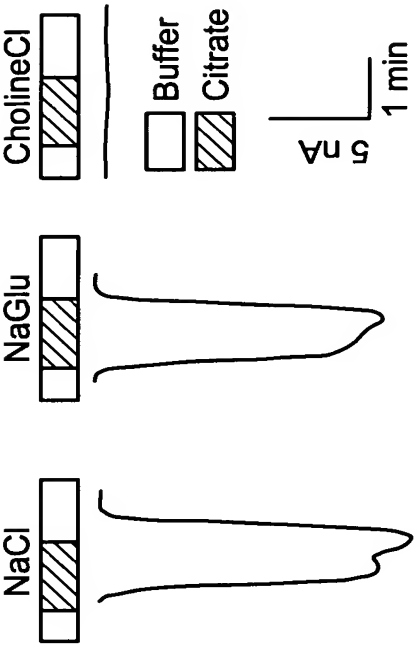


Fig. 24C

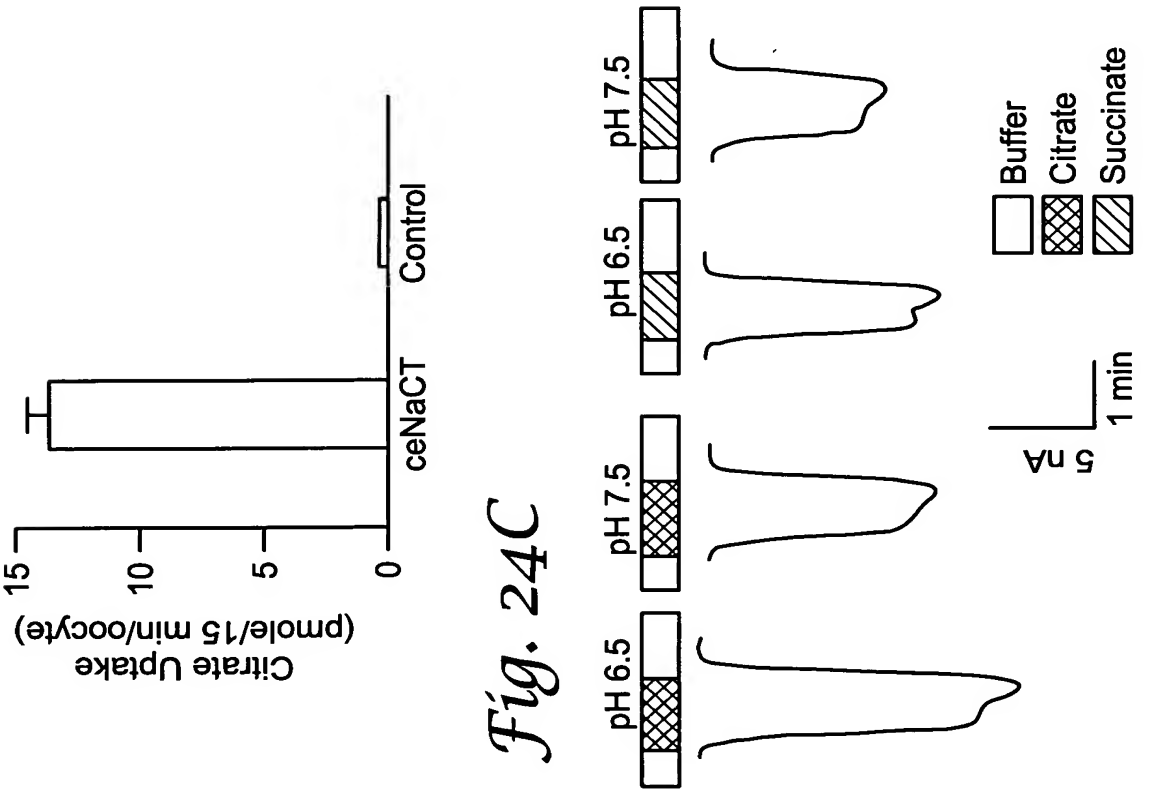


Fig. 24D

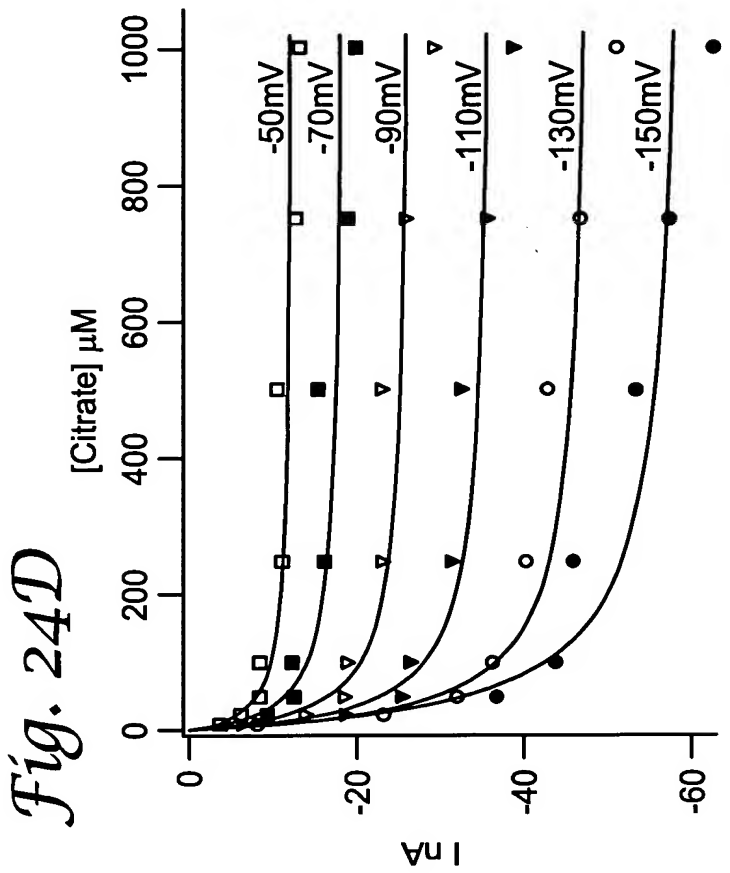


Fig. 25A

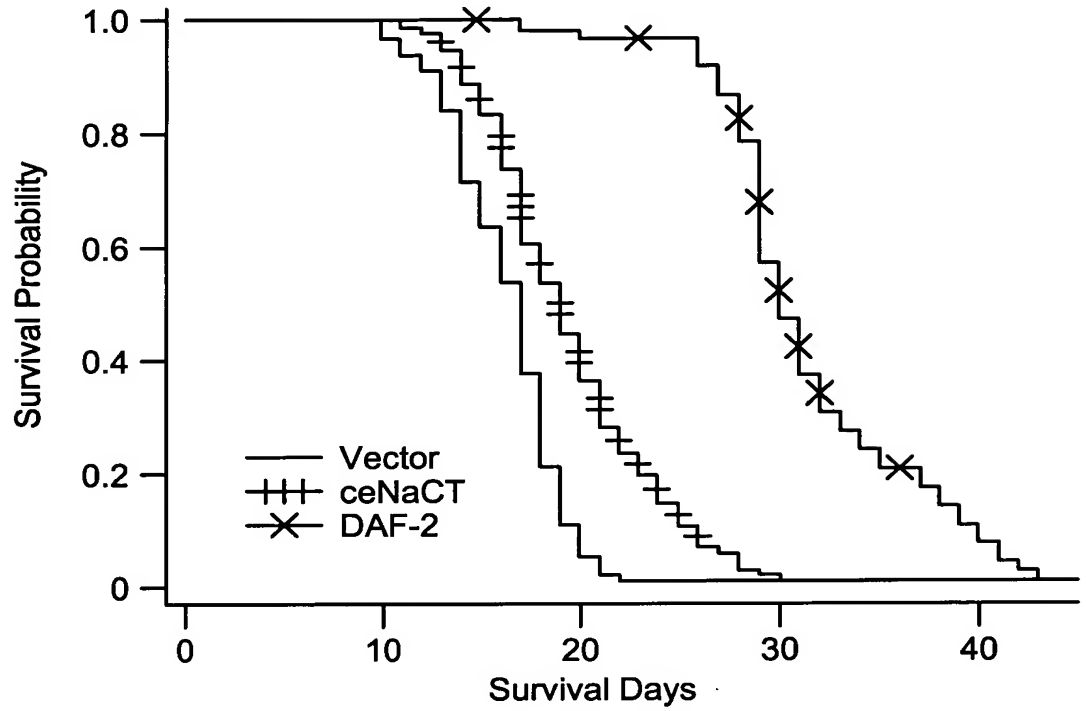
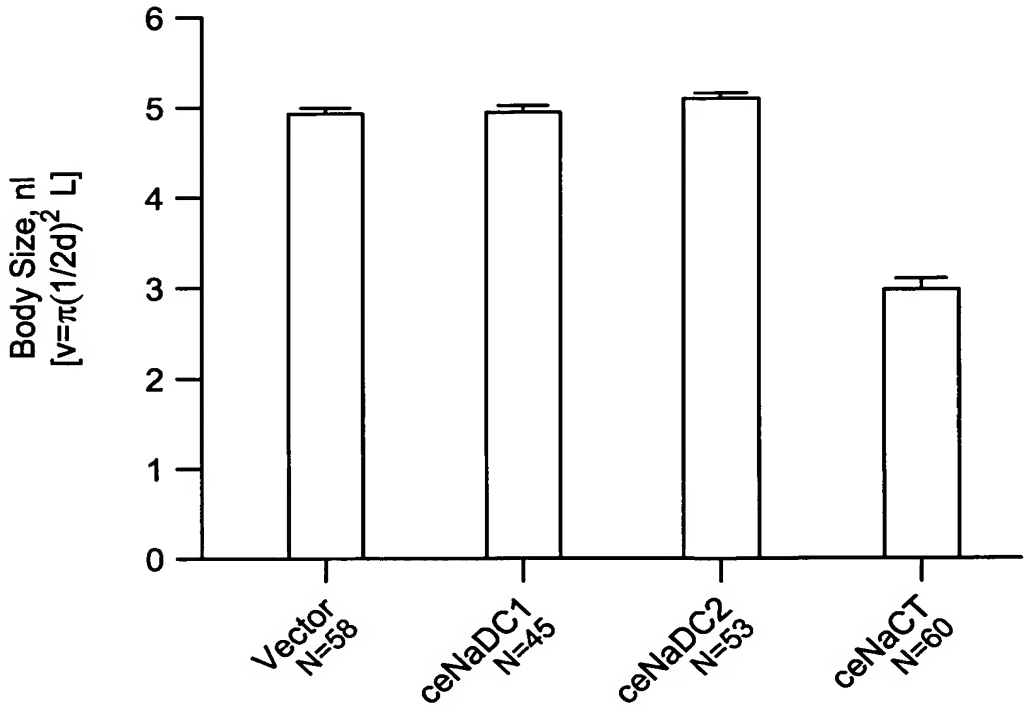


Fig. 25B



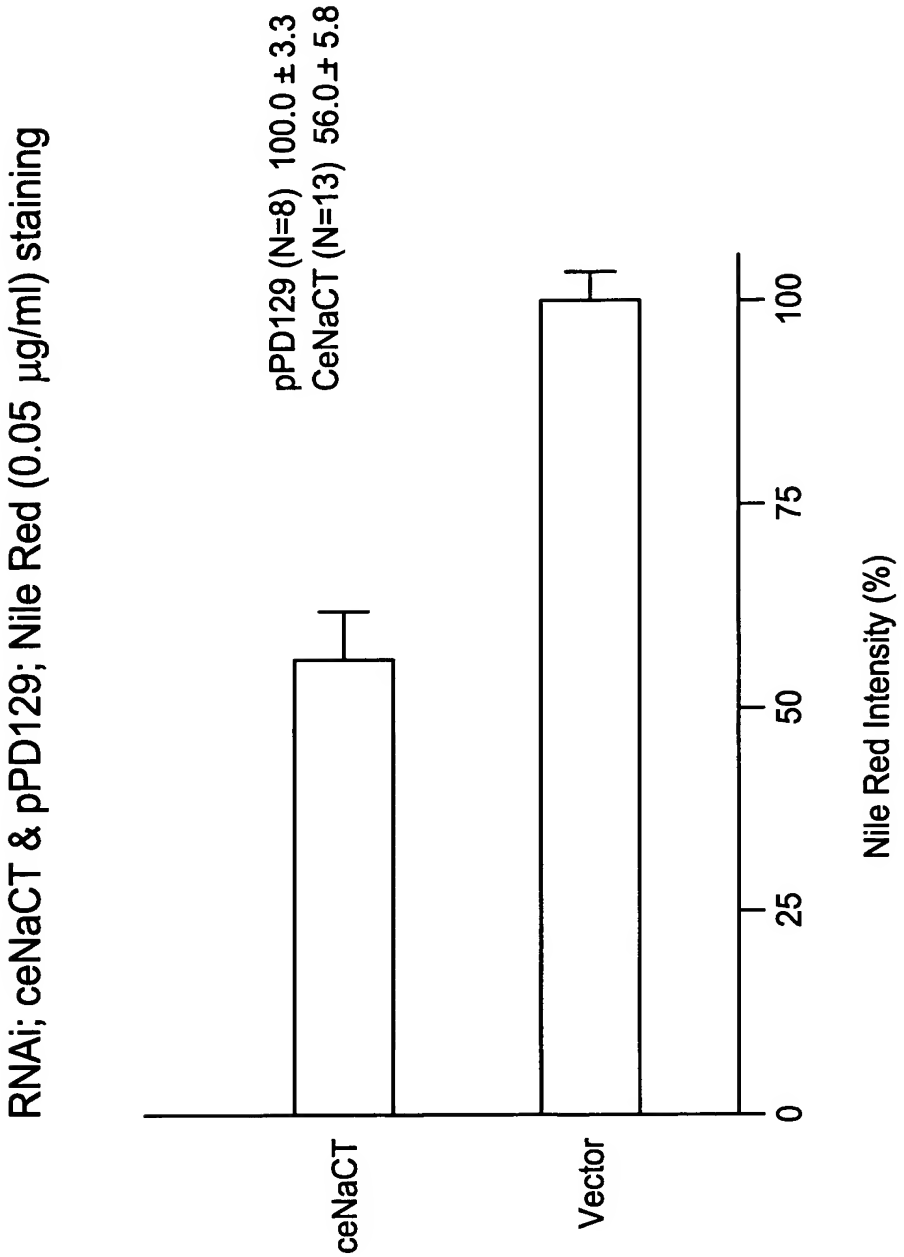

RNAi; ceNaCT & pPD129; Nile Red (0.05 µg/ml) staining
pPD129 (N=8) 100.0 ± 3.3
CeNaCT (N=13) 56.0± 5.8
Nile Red Intensity (%)
0
25
50
75
100
ceNaCT
Vector

Fig. 26

Fig. 27

Mouse NaCT sequence
cDNA sequence (16 nt + 1719 nt)
SEQ ID NO: 9

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Protein sequence(572 nt)
SEQ ID NO: 10

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FLSVNTWGRAMFNLDNFPDWANSTSVNT

Fig. 28A

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rat       1 MASAKTYVTKFKSFVILFFAPILLLPLIILVPDKFARCAYVIILMAIYWCTDVIPVAITS
human     1 MASALSYVSKFKSFVILFVTPLLLLPLVILMPAKFVRCAYVIILMAIYWCTEVIPLAVTS

mouse    61 LLPVLLFPLLKVLDSKQVCIQYMKDTNMLFLGSLIVAVAVERWKLHKRVALRMLLFVGTK
rat      61 LLPVLLFPLLKVLDSKQVCVQYMLDTNMLFLGSLIVATAVERWELHKRIALRMLLFVGTK
human    61 LMPVLLFPLFQILDSRQVCVQYMKDTNMLFLGGLIVAVAVERWNLHKRIALRTLLWVGAK

mouse   121 PSRLMLGFMFVTAFLSMWISNTAATAMMIPIVEAMLQQMIAANTAVEASLGTLELLDKNK
rat     121 PSRLMLGFMFVTAFLSMWISNTATTAMMIPIVEAMLEQMVATNVAVDASQRTMELLDKNK
human   121 PARLMLGFMGVTALLSMWISNTATTAMMVPIVEAILQQMEATSAATEAG---LELVDKGK

mouse   181 TSELPGSQVVFEDPNVQEQEDEETKNMYKAMHLCVCYSASIGGTATLTGTGPNVVLLGQM
rat     181 ASELPGSQVVFEDPSVQKQEDEETKNMYKAMNLCVCYAASIGGTATLTGTGPNVVLLGQM
human   178 AKELPGSQVIFEGPTLGQQEDQERKRLCKAMTLCICYAASIGGTATLTGTGPNVVLLGQM

mouse   241 QELFPDSKDVLNYASWFGFAFPNMVMMLVLAWLWLQCLYMRFNLKKTCICCGEKKRDTEK
rat     241 QELFPDSKDVMNFASWFAFALPNMLLMLVMAWLWLLCFYMRPNLKKTCICCGRKKKDTEK
human   238 NELFPDSKDLVNFASWFAFAFPNMLVMLLFAWLWLQFVYMRFNFKKSWGCGLESKK-NEK

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rat     301 IASKVLYEEYRKLGPLSYAECNVLFCFGLLIILWFSRDPGFMPGWLSIAWIEGNTKHVTD
human   297 AALKVLQEEYRKLGPLSFAEINVLICFFLLVILWFSRDPGFMPGWLTVAWVEGETKYVSD

mouse   361 ATVAIFVAILLFIIPSQKPKFNFSSQTEEERKTPFYPPALLDWKVAQEKVPWDIVLLLGG
rat     361 ATVAIFVAILLFIVPSQKPKFNFSRQTEEERKTPFYPPPLLNWKVTQEKVPWGIVLLLGG
human   357 ATVAIFVATLLFIVPSQKPKFNFRSQTEEERKTPFYPPPLLDWKVTQEKVPWGIVLLLGG

mouse   421 GFAMAKGCETSGLSKWMAAQMEPLRLVKPAVITLILSCLVAMTTECTSNVATTTLFLPIF
rat     421 GFAMAKGCETSGLSEWMARQMEPLSSVRPAIITLILSCIVAMTTECTSNVATTTLFLPIF
human   417 GFALAKGSEASGLSVWMGKQMEPLHAVPPAAITLILSLLVAVFTECTSNVATTTLFLPIF

mouse   481 ASMARSIGIHPLYVMIPCTMSASLAFMLPVATPPNAIVFAYGHLRVVDMMKTGLIMNFVG
rat     481 ASMARSIGIHPLYVMIPCTLSASLAFMLPVATPPNAIVFAYGHLKVIDMVKTGLVMNILG
human   477 ASMSRSIGLNPLYIMLPCTLSASFAFMLPVATPPNAIVFTYGHLKVADMVKTGVIMNIIG

mouse   541 ILSVFLSVNTWGRAMFNLDNFPDWANSTSVNT
rat     541 IASVFLSVNTWGRAVFNLDKFPDWANLTHINT
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Fig. 28B

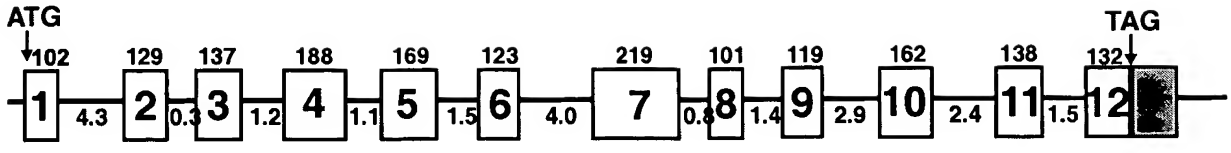
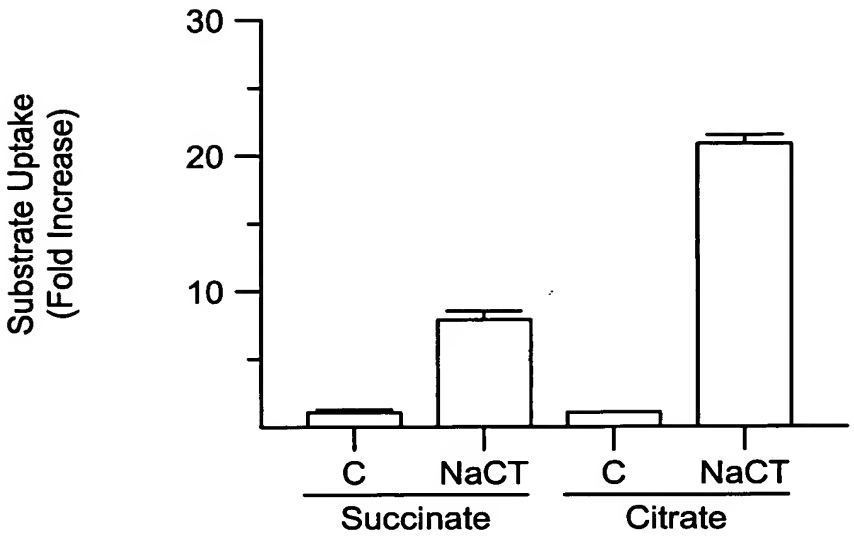


Fig. 29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(Fold Increase)
30
20
10
C
NaCT
C
NaCT
Succinate
Citrate

Fig. 30A

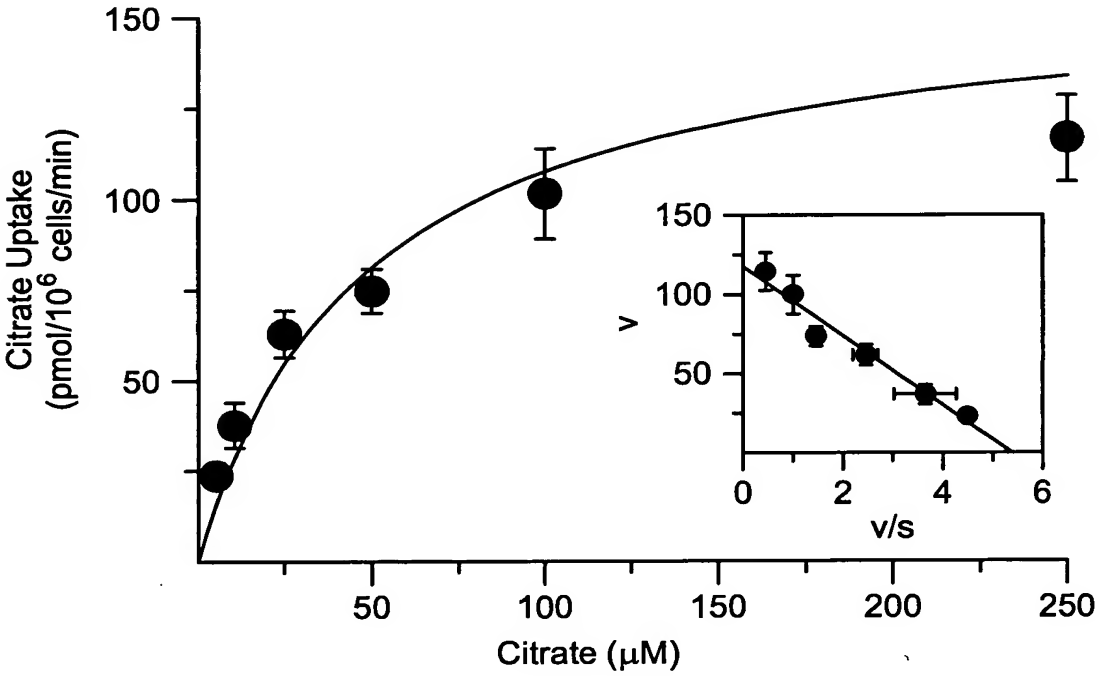


Fig. 30B

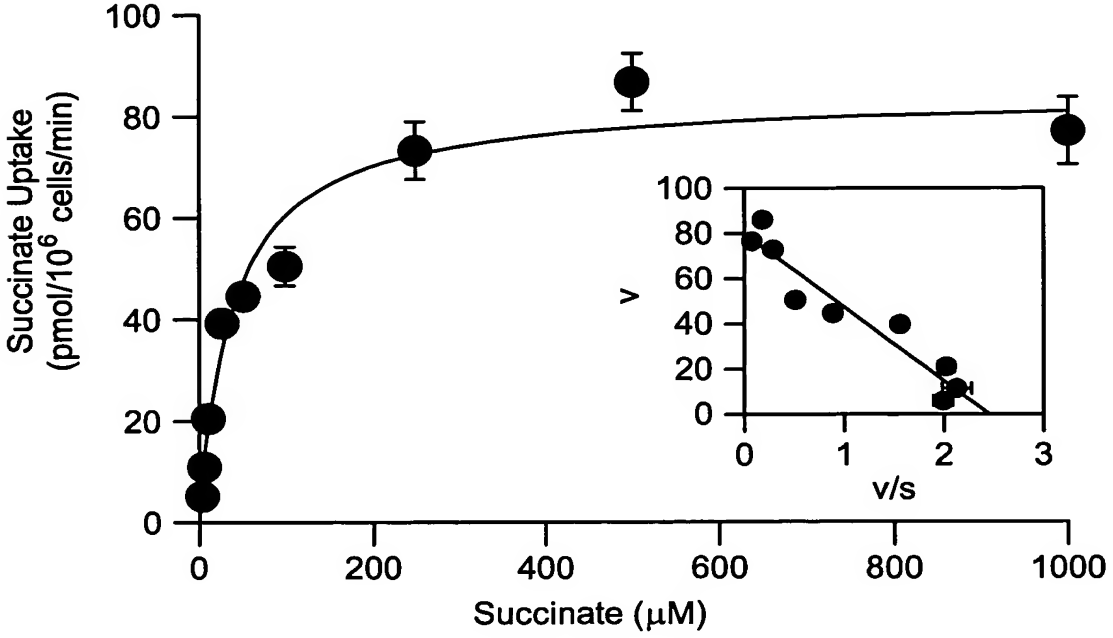


Fig. 31A

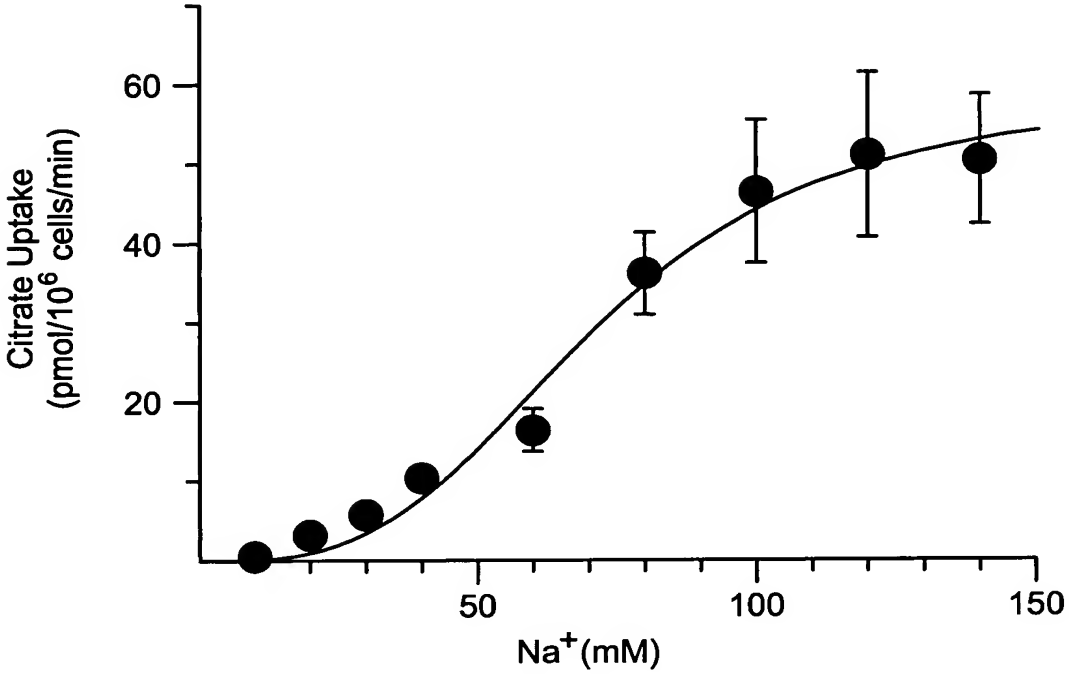


Fig. 31B

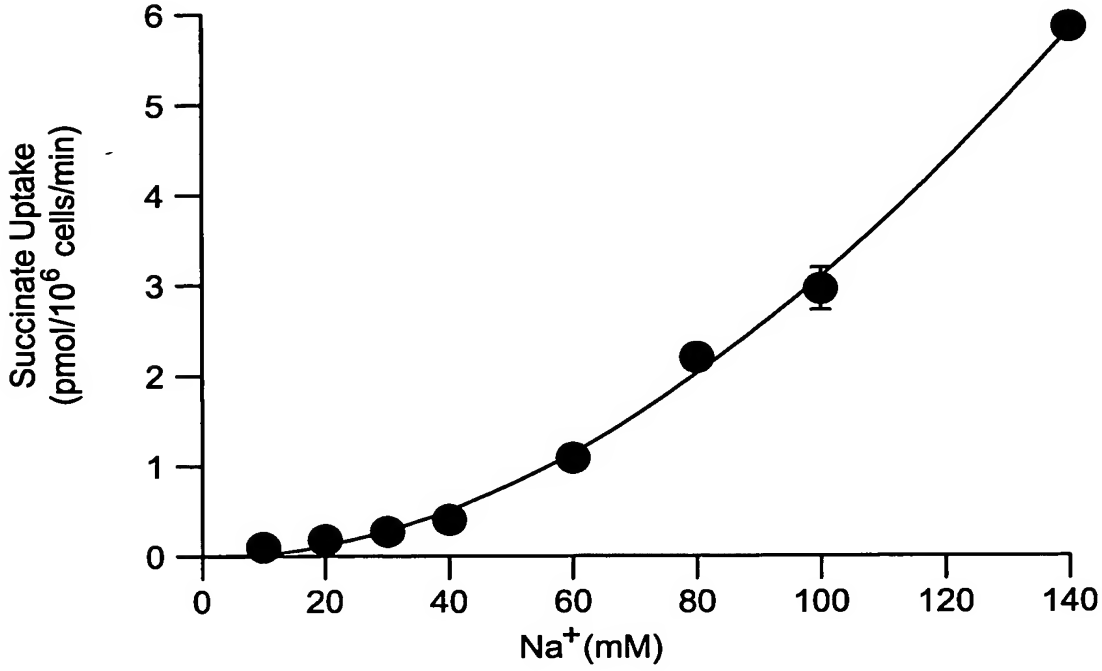


Fig. 32

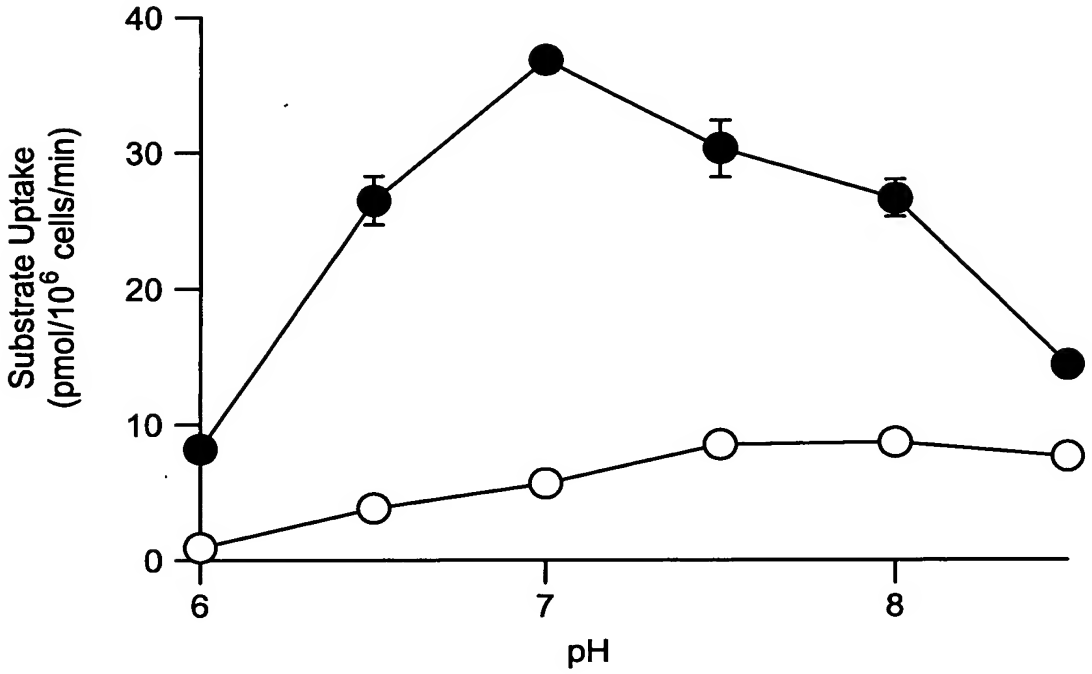
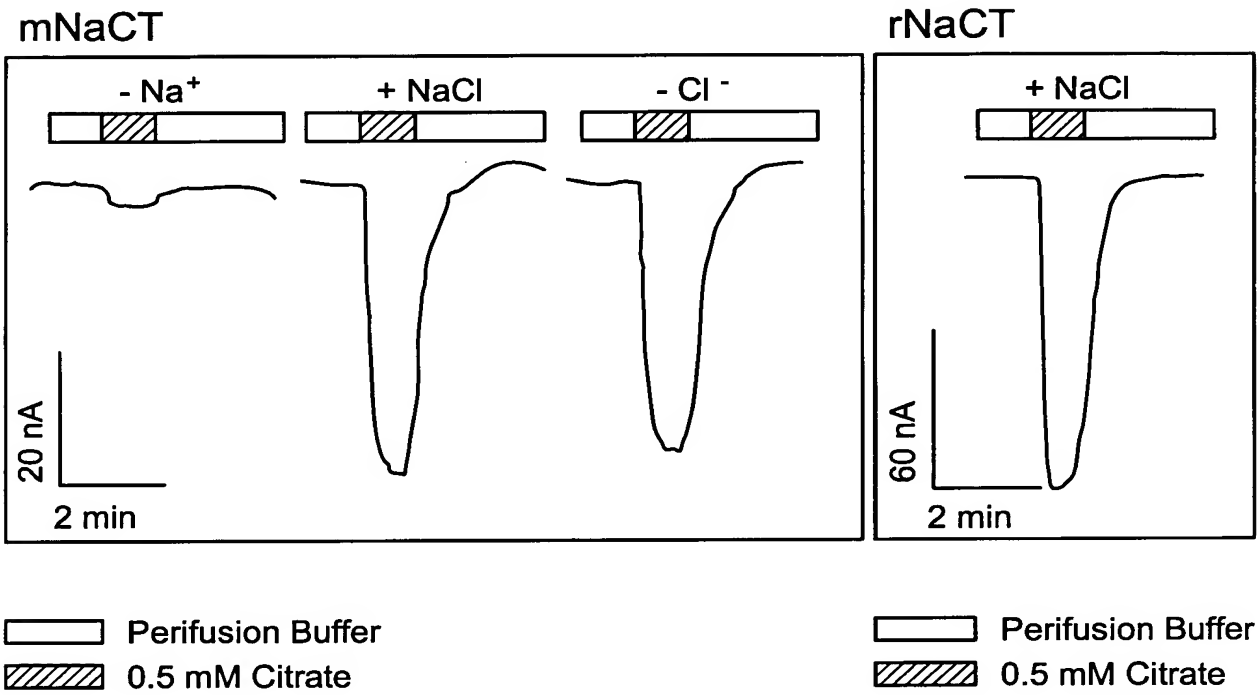


Fig. 33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rNaCT
- Na+
+ NaCl
- Cl -
+ NaCl
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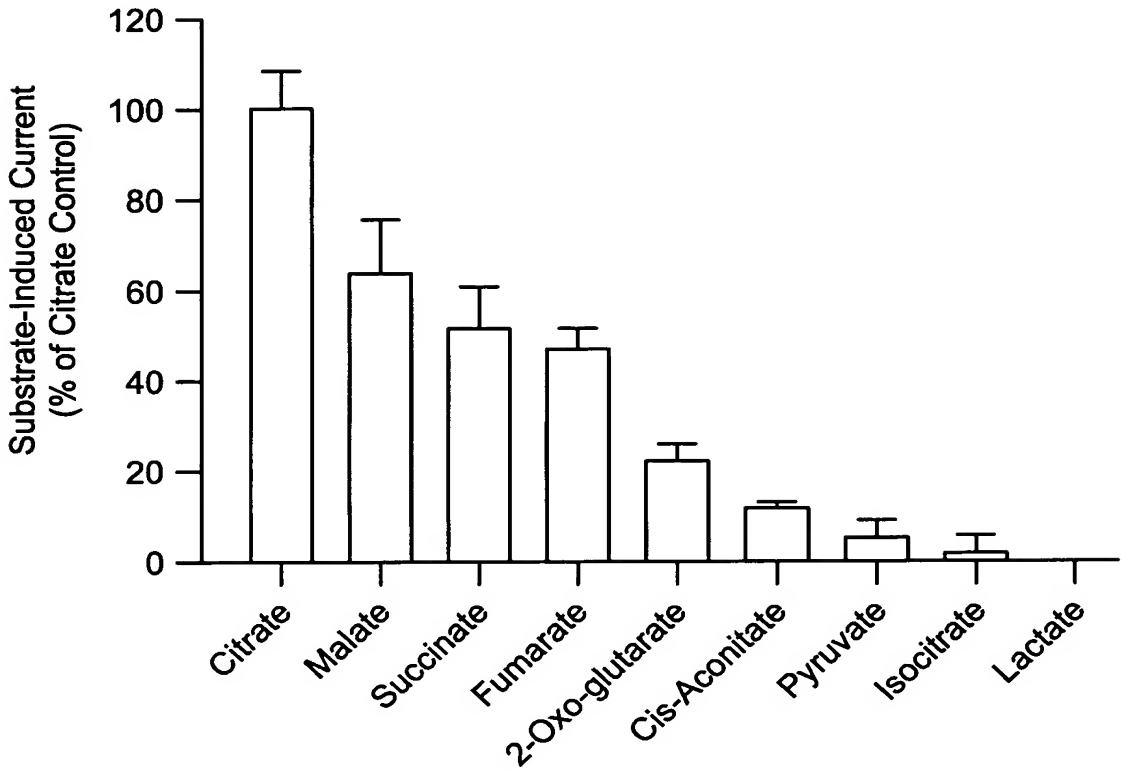
2 min
60 nA
2 min
Perifusion Buffer
0.5 mM Citrate
Perifusion Buffer
0.5 mM Citrate

Fig. 34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(% of Citrate Control)
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100
80
60
40
20
0
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Malate
Succinate
Fumarate
2-Oxo-glutarate
Cis-Aconitate
Pyruvate
Isocitrate
Lactate

Fig. 35A

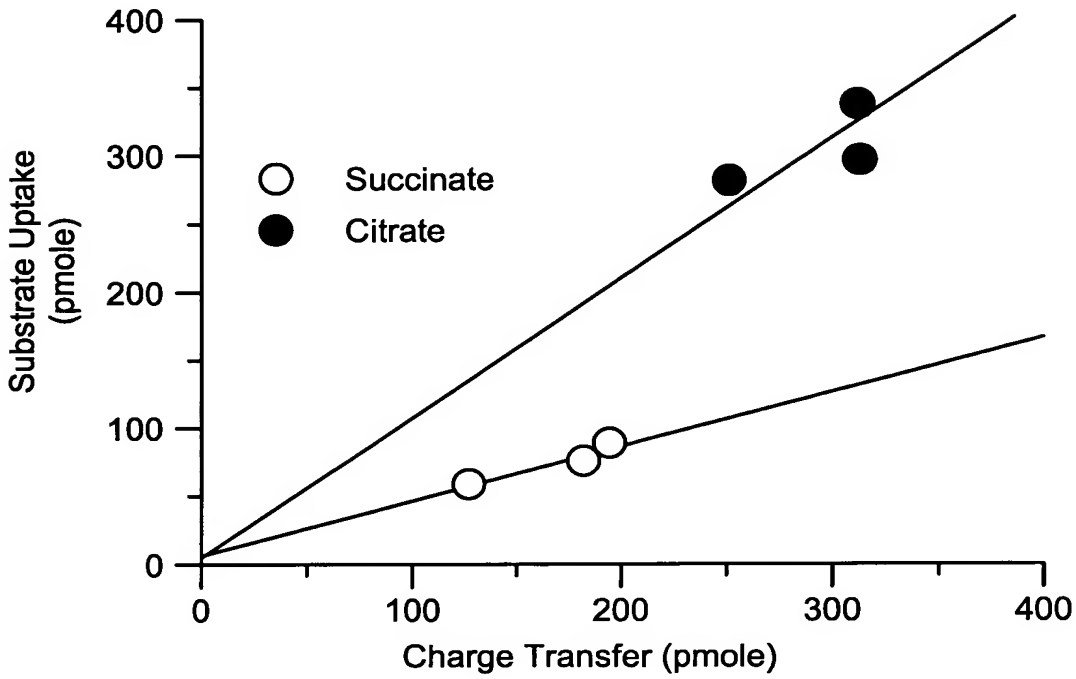

Fig. 35B

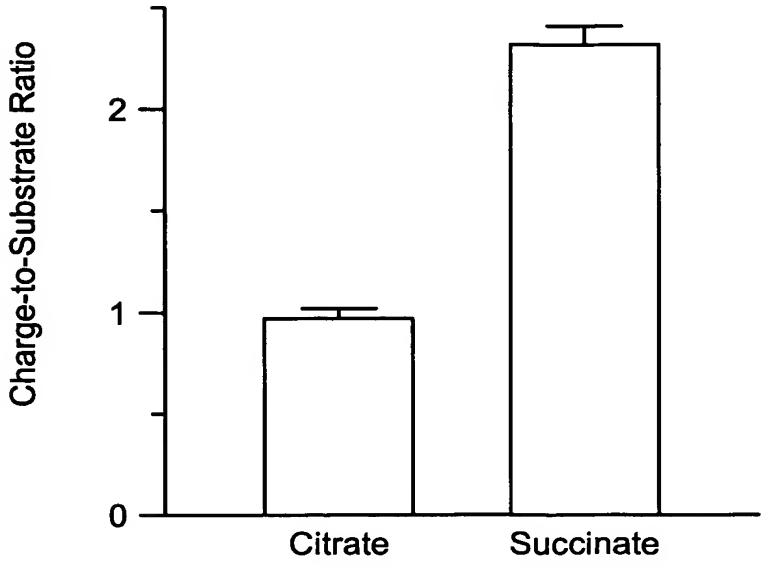

Fig. 36

Zebra Fish NaCT full length cDNA (1#) (1-2536 + 15 bp)
ORF: from 76 – 1824 (length = 1749)
SEQ ID NO: 11

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Amino Acid Sequence (581 aa)
SEQ ID NO: 12

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VFPSKPPRLCFWRTESFDTVPQQESGPTPALLTWKVTQKKMPWSIILLLGGGFALAKGSEISGLSKWLGDQMSPLQ
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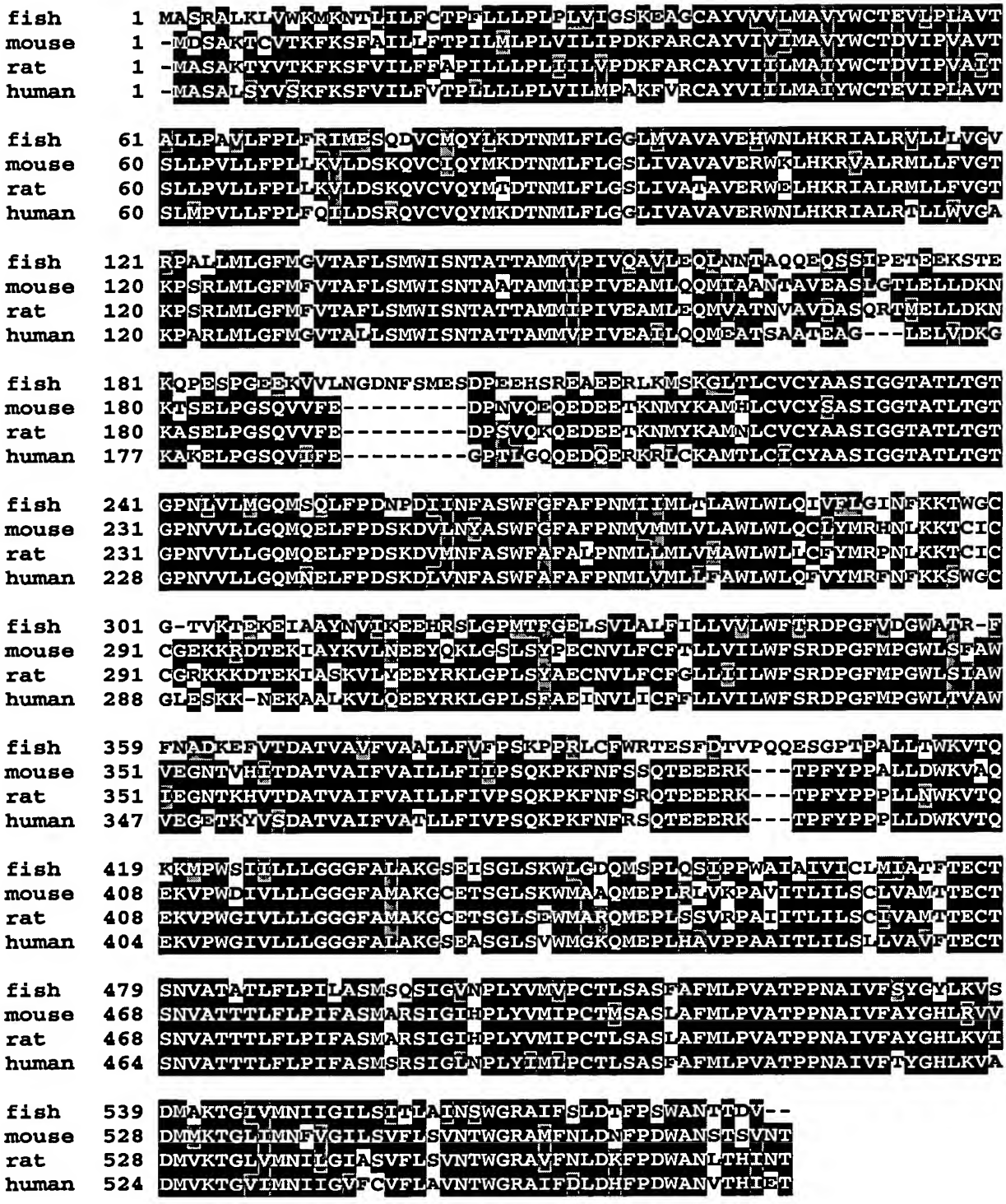
Fig. 37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rat 1 -MASAKTYVTKFKSFVILFFAPILLLPLIILVPDKFARCAYVIILMAIYWCTDVIPVAIT
human 1 -MASALSYVSKFKSFVILFVTPLLLLPLVILMPAKFVRCAYVIILMAIYWCTEVIPLAVT
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mouse 60 SLLPVLLFPLLKVLDSKQVCIQYMKDTNMLFLGSLIVAVAVERWKLHKRVALRMLLFVGT
rat 60 SLLPVLLFPLLKVLDSKQVCVQYMTDTNMLFLGSLIVATAVERWELHKRIALRMLLFVGT
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mouse 291 CGEKKRDTEKIAYKVLNEEYQKLGSLSYPECNVLFCFTLLVILWFSRDPGFMPGWLSFAW
rat 291 CGRKKKDTEKIASKVLYEEYRKLGPLSYAECNVLFCFGLLIILWFSRDPGFMPGWLSIAW
human 288 GLESKK-NEKAALKVLQEEYRKLGPLSFAEINVLICFFLLVILWFSRDPGFMPGWLTVAW
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human 404 EKVPWGIVLLLGGGFALAKGSEASGLSVWMGKQMEPLHAVPPAAITLILSLLVAVFTECT
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mouse 528 DMMKTGLIMNFVGILSVFLSVNTWGRAMFNLDNFPDWANSTSVNT
rat 528 DMVKTGLVMNILGIASVFLSVNTWGRAVFNLDKFPDWANLTHINT
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Fig. 38A

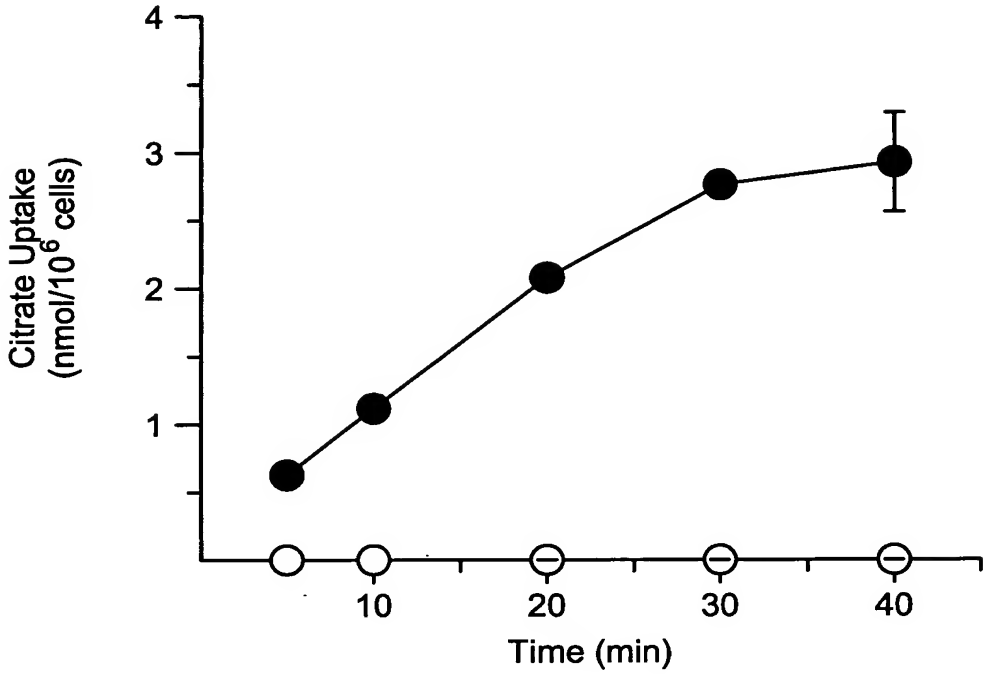


Fig. 38B

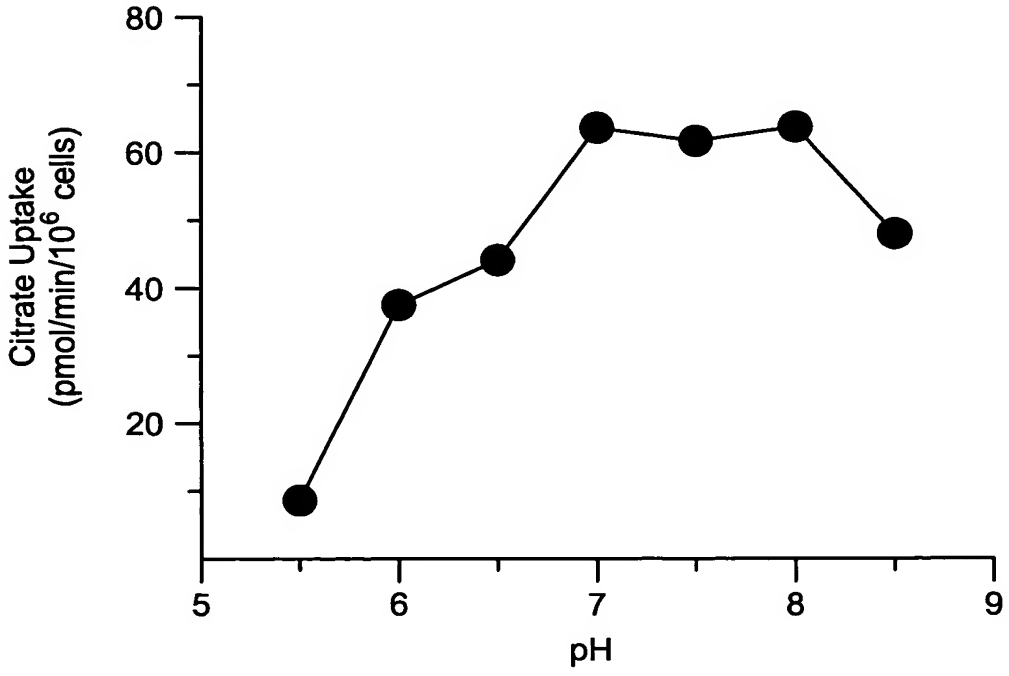


Fig. 39A

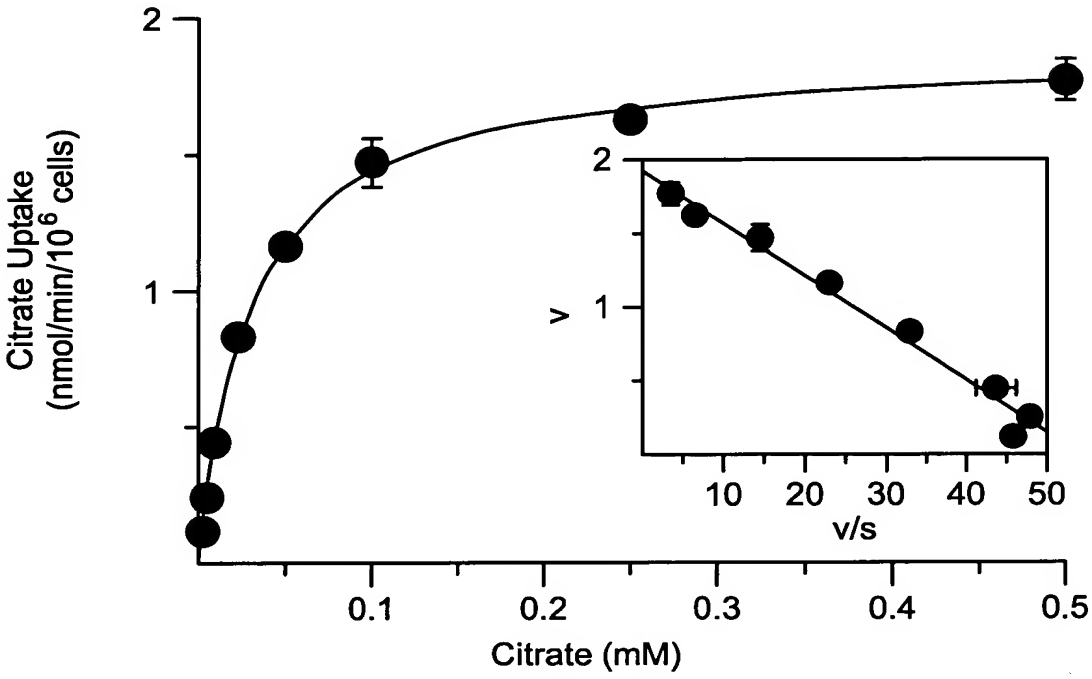


Fig. 39B

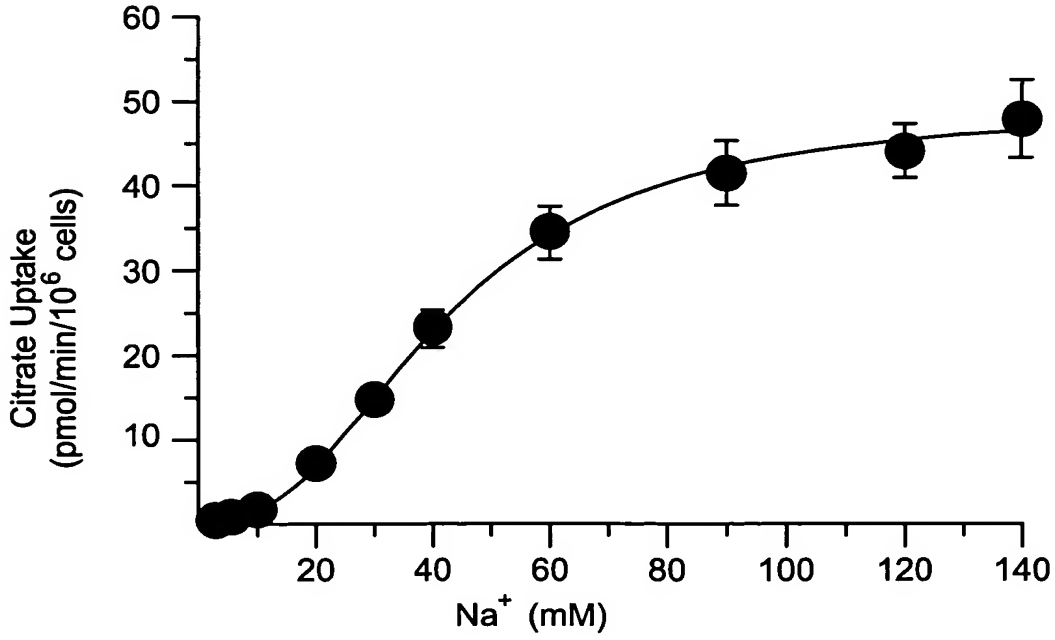


Fig. 40A

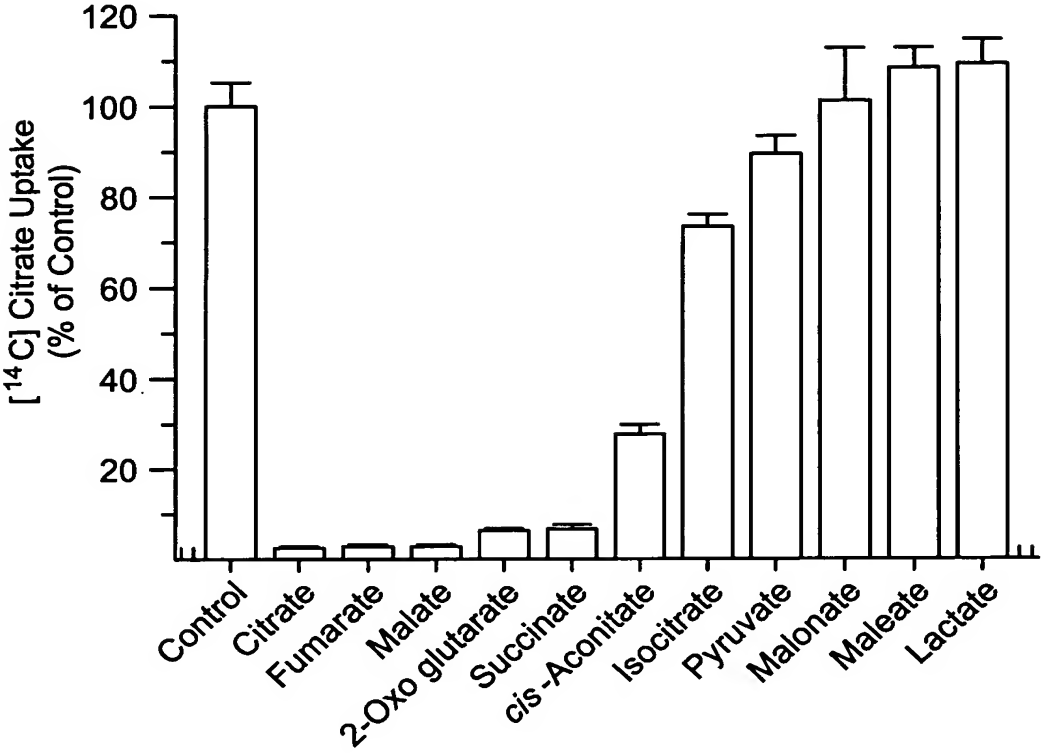


Fig. 40B

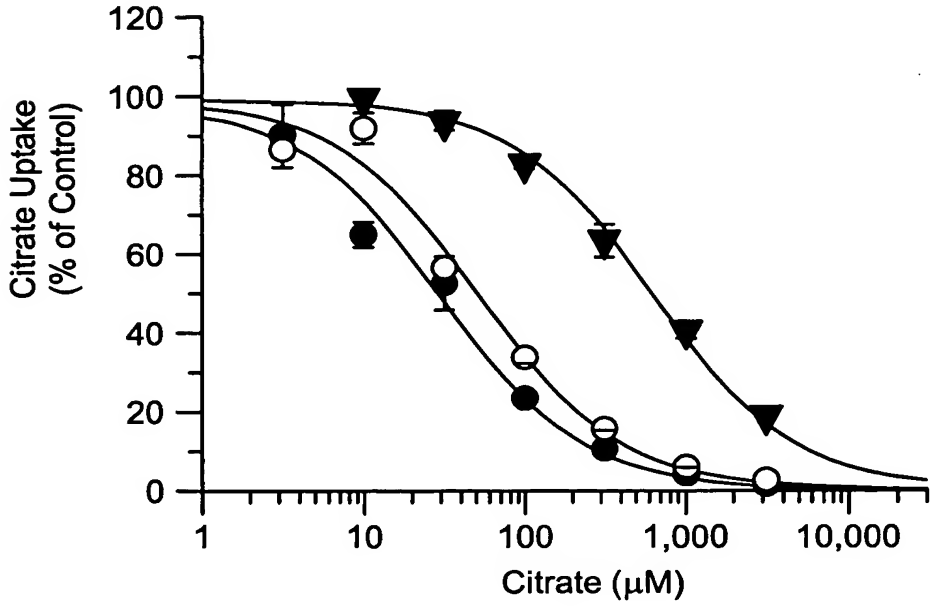


Fig. 41

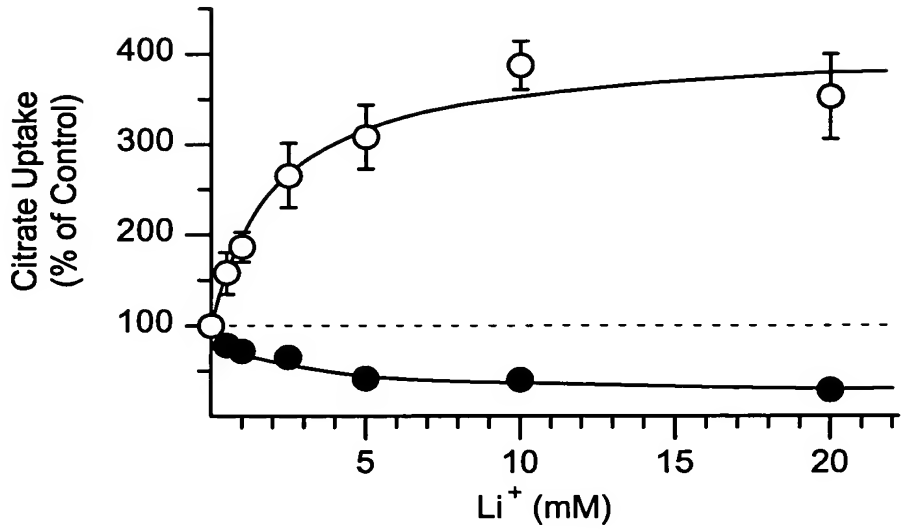


Fig. 42A

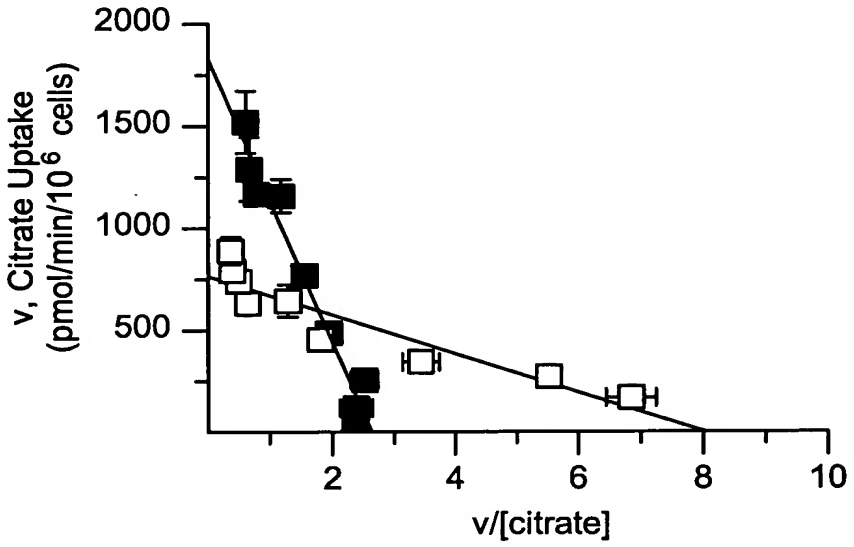


Fig. 42B

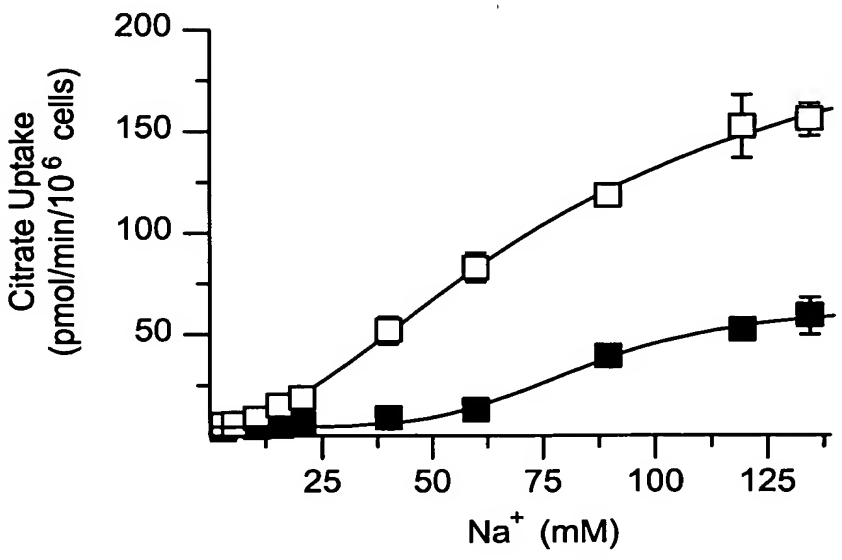


Fig. 43A

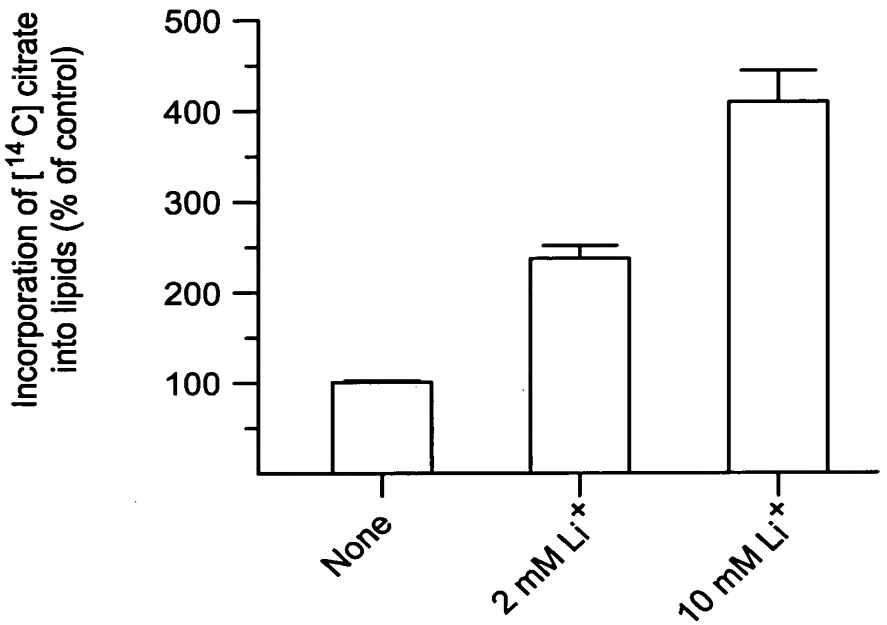
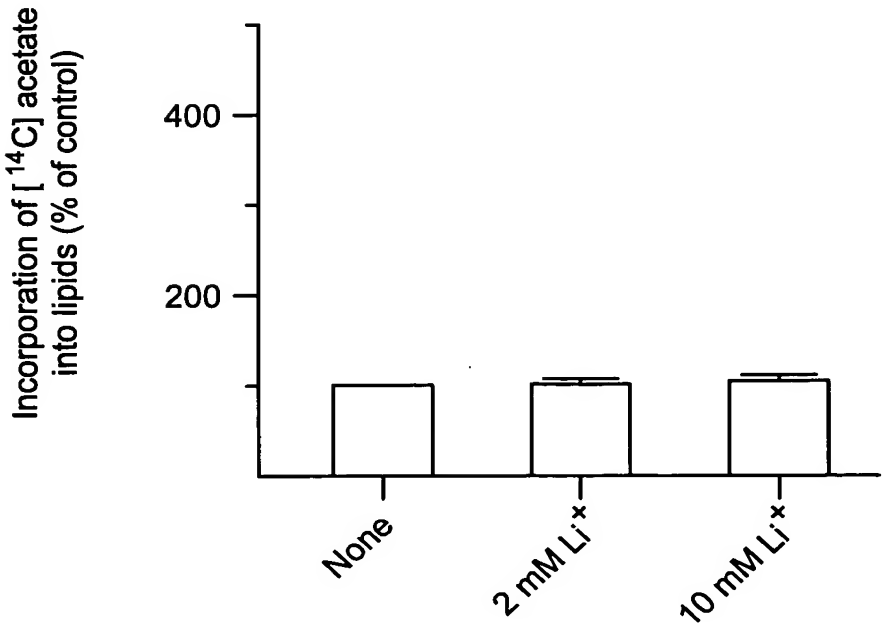
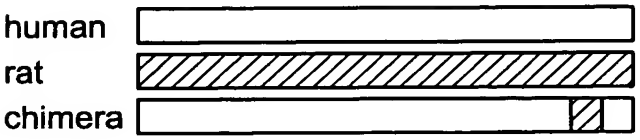


Fig. 43B



45/45

Fig. 44A



	-Li+	+Li+	ratio
	Citrate uptake (pmol/min/10^6 cells)		
human	21.8 ± 2.5	70.5 ± 4.6	3.23
rat	88.7 ± 6.5	21.8 ± 2.5	0.42
chimera	116.4 ± 5.3	111.1 ± 5.0	0.95

Fig. 44B

	500		516
human	LSAS**F**AFMLPVATPPNAIVF**T**		
rat	LSAS**L**AFMLPVATPPNAIVF**A**		
	504		520

Fig. 44C

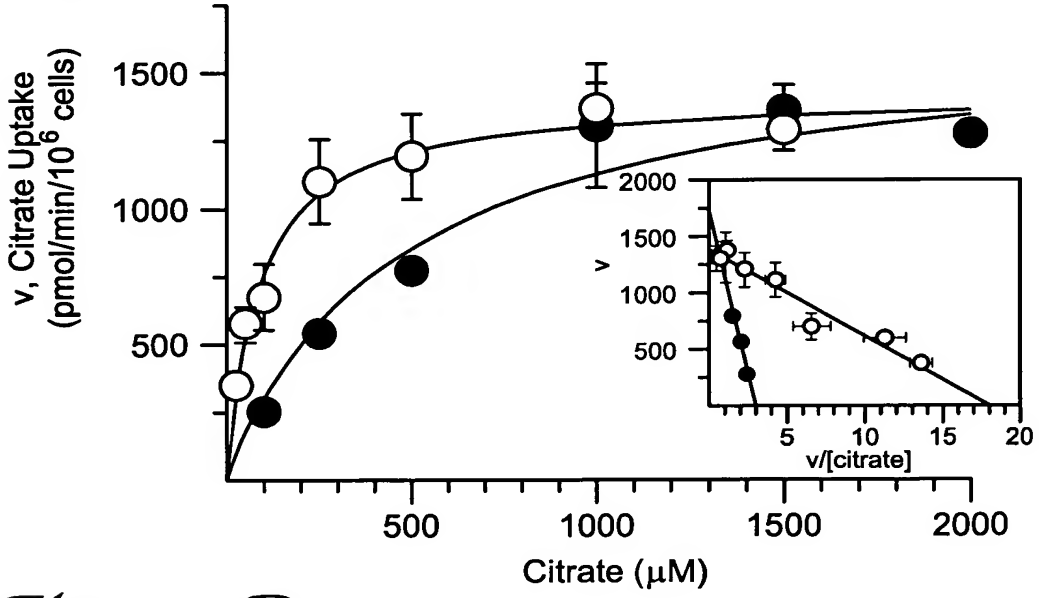
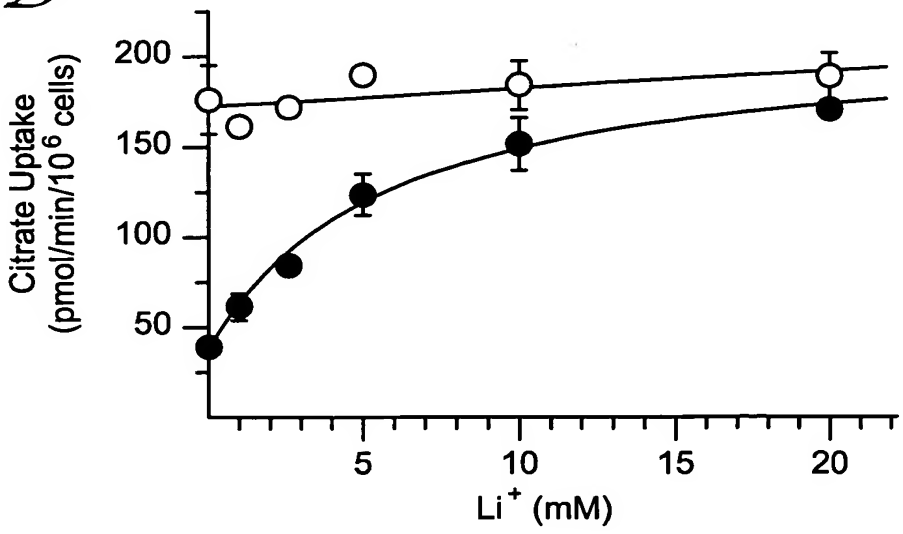



Fig. 44D